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(21) International Application Number: PCT/US98/16458 (22) International Filing Date: 18 August 1998 (18.08.98) (30) Priority Data: 60/055,916                      18 August 1997 (18.08.97)                      US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US    60/055,916 (CON) Filed on                                      18 August 1997 (18.08.97) (71) Applicant (for all designated States except US): CENTAUR PHARMACEUTICALS, INC. [US/US]; 484 Oakmead Parkway, Sunnyvale, CA 94086 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): KELLEHER, Judith, A. [US/US]; 34701 Woodhue Terrace, Fremont, CA 94555 (US). MAPLES, Kirk, R. [US/US]; 2170 Stratton Place, San Jose, CA 95131 (US). ZHANG, Yong-Kang [CN/US]; Apartment 16, 3430 Warburton Avenue, Santa Clara, CA 95051 (US).		(74) Agents: BENZ, William, H. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.									
(54) Title: FURANSULFONIC ACID DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME											
<table border="1"> <caption>Acquisition Data from Bar Chart</caption> <thead> <tr> <th>Strain/Treatment</th> <th>Acquisition</th> </tr> </thead> <tbody> <tr> <td>+ +/1% MC</td> <td>~1.3</td> </tr> <tr> <td>Fas<sup>+</sup>/1% MC</td> <td>~0.4</td> </tr> <tr> <td>Fas<sup>+</sup>/Compound 1</td> <td>~1.2</td> </tr> </tbody> </table>				Strain/Treatment	Acquisition	+ +/1% MC	~1.3	Fas <sup>+</sup> /1% MC	~0.4	Fas <sup>+</sup> /Compound 1	~1.2
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(57) Abstract											
; Disclosed are furansulfonic acid derivatives and pharmaceutical compositions containing such derivatives. The disclosed compositions are useful for preventing and/or treating neurodegenerative, autoimmune and inflammatory conditions in mammals.											

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**FURANSULFONIC ACID DERIVATIVES  
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME**

**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of U.S. Provisional Application No. 60/055,916, filed August 18, 1997, which application is incorporated herein by reference in its entirety.

**BACKGROUND OF THE INVENTION**

Field of the Invention

This invention relates to novel furansulfonic acid derivatives and to pharmaceutical compositions containing such derivatives. This invention also relates to methods for preventing and/or treating neurodegenerative, autoimmune  
5 and inflammatory conditions in mammals using furansulfonic acid derivatives.

State of the Art

Alzheimer's disease is a neurodegenerative condition in which nerve cells in the brain are systematically destroyed resulting in progressive memory loss,  
10 mental confusion and ultimately death. The National Institute on Aging (NIA) has recently estimated that about 4 million people in the United States are currently afflicted with Alzheimer's disease. At present, there is no treatment that effectively prevents the disease or reverses the progressive degeneration.

15 In recent years, significant progress has been made in understanding the pathogenesis of Alzheimer's disease. For example, it is now known that patients with Alzheimer's disease develop amyloid plaque deposits around and between the nerve cells of their brain. These plaque deposits are made up of fibrillar aggregates of a small peptide called amyloid  $\beta$ -peptide or A $\beta$ . The plaque deposits initially  
20 form in the hippocampus and cortex regions of the brain (areas associated with memory and cognition) and then spread to other areas as the disease progresses. The deposition of fibrils and plaques is also followed by inflammation of the

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surrounding support cells, called glia, which may lead to further loss of neurons. Eventually, the nerve cells in the brains of most Alzheimer's patients develop tangles of a microtubule-associated protein, called tau, which are believed to be a response by the nerve cells to damage.

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Progress in understanding the underlying mechanisms of Alzheimer's disease has led to the development of various *in vitro* and *in vivo* models to identify compounds effective for preventing and/or treating Alzheimer's disease and other neurodegenerative conditions. In one such *in vitro* model, compounds are evaluated for their ability to intervene in A $\beta$ (1-40) or A $\beta$ (1-42) beta-pleated sheet formation. Since the deposition of amyloid  $\beta$ -peptide is associated with the development of Alzheimer's disease, compounds which effectively disrupt the formation of A $\beta$ (1-40) or A $\beta$ (1-42) beta-pleated sheets are potentially useful for preventing and/or reversing Alzheimer's disease-related amyloid deposits.

15

In another *in vitro* model, compounds are evaluated for their ability to protect against A $\beta$ (25-35)-induced neuronal cell loss in rat embryonic hippocampal neuronal/astrocytes cultures. As discussed above, patients with Alzheimer's disease suffer a progressive loss of neuronal cells. Accordingly, compounds which are effective in this *in vitro* test are potentially useful for reducing or preventing neuronal cell loss in patients afflicted with Alzheimer's disease or other neurodegenerative conditions.

20

A third *in vitro* Alzheimer's disease model is based on the observation that  $\beta$ -amyloid increases the release of cytokines, such as interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), in human monocyte cells. IL-1 $\beta$ , IL-6 and TNF $\alpha$  are proteins associated with inflammatory and immune responses. As previously mentioned, the deposition of fibrils in the brains of Alzheimer's patients is associated with inflammation of the surrounding support cells. See, S. D. Yan et al., *Proc. Natl. Acad. Sci. USA*, **94**, 5296 (1997). Thus, compounds effective in this *in vitro* test are potentially useful for reducing and/or preventing the inflammation associated with Alzheimer's disease.

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Additionally, elevated levels of IL-1 $\beta$ , IL-6, TNF $\alpha$  and other cytokines are associated with a wide variety of inflammatory and autoimmune conditions, including septic shock, rheumatoid arthritis, erythema nodosum leprosy, meningococcal meningitis, multiple sclerosis, systemic lupus and the like. *See*, L. Sekut et al., *Drug News Perspect.* **1196**, 9, 261; and A. Waage et al., *J. Exp. Med.* **1989**, 170, 1859-1867. Accordingly, compounds which inhibit the production of such cytokines are potentially useful for treating such inflammatory and autoimmune conditions.

Similarly, various *in vivo* disease models are available for identifying compounds useful for preventing and/or treating neurodegenerative, autoimmune and inflammatory conditions. One such *in vivo* disease model is based on the observation that mammals suffer locomotor impairment when A $\beta$ (25-35) is injected into the substantia nigra region of their brain. Since amyloid  $\beta$ -peptide deposits are associated with Alzheimer's disease, compounds which effectively reduce the locomotor impairment of mammals injected with A $\beta$ (25-35) are potentially useful for the prevention and/or treatment of Alzheimer's disease and other neurodegenerative conditions. Another *in vivo* disease model is based on the observation that certain strains of autoimmune mice develop cognitive deficits as they mature. *See*, for example, Forster et al., *Behav. Neural Biology* **1988**, 49, 139-151. Thus, compounds which prevent or reduce such cognitive deficits are potentially useful for preventing and/or treating neurodegenerative and autoimmune conditions.

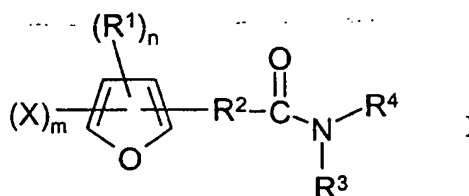
It has now been discovered that certain novel furansulfonic acid derivatives effectively inhibit the formation of A $\beta$ (1-40) beta-pleated sheets and/or protect against neuronal cell loss and/or inhibit the release of cytokines, such as IL-1 $\beta$ , IL-6 and TNF $\alpha$ . Additionally, in *in vivo* tests, such compounds have been found to reduce the locomotor impairment caused by A $\beta$ (25-35) and to reduce the cognitive deficits that develop in certain strains of autoimmune mice.

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## SUMMARY OF THE INVENTION

This invention provides novel furansulfonic acid derivatives which are useful for preventing and/or treating neurodegenerative, autoimmune and inflammatory conditions in mammals. In particular, the compounds of this invention are useful for preventing and/or treating Alzheimer's disease.

Accordingly, in one of its composition aspects, this invention is directed to compounds of formula I:



15 wherein

each R<sup>1</sup> is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

R<sup>2</sup> is selected from the group consisting of alkylene, alkenylene and a covalent bond;

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that R<sup>3</sup> and R<sup>4</sup> are not both hydrogen; or R<sup>3</sup> and R<sup>4</sup> can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

each X is independently selected from the group consisting of -SO<sub>3</sub>Y and -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, wherein Y is hydrogen or a pharmaceutically acceptable cation, and R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl; or R<sup>5</sup> and R<sup>6</sup> can be joined together to form a cycloalkyl ring of from 4 to 10

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carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;  $m$  is an integer from 1 to 3; and  $n$  is an integer from 0 to 2, provided that  $m + n = 3$ .

5

Preferably, in the compounds of formula I above,  $R^1$  is selected from the group consisting of hydrogen and alkyl. More preferably,  $R^1$  is hydrogen.

10

$R^2$  is preferably selected from the group consisting of an alkylene group of the formula  $-(CH_2)_p-$ , wherein  $p$  is an integer from 1 to 6; an alkenylene group of the formula  $-CR^7=CR^8-$ , wherein  $R^7$  and  $R^8$  are independently selected from the group consisting of hydrogen and lower alkyl; and a covalent bond. More preferably,  $R^2$  is selected from the group consisting of  $-CH_2CH_2-$ ,  $-CH=CH-$  and a covalent bond.

15

Preferably,  $R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, provided that  $R^3$  and  $R^4$  are not both hydrogen. Alternatively,  $R^3$  and  $R^4$  are preferably joined together to form a cycloalkyl group having 4 or 6 carbon atoms. More preferably,  $R^3$  is hydrogen and  $R^4$  is lower alkyl or cycloalkyl. Still more preferably,  $R^3$  is hydrogen and  $R^4$  is isopropyl,  $n$ -butyl or cyclohexyl.

20

$X$  is preferably  $-SO_3Y$  or  $-SO_2NR^5R^6$ , where  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl and cycloalkyl.

25

Alternatively,  $R^5$  and  $R^6$  are preferably joined together to form a cycloalkyl ring having 4 to 6 carbon atoms. More preferably, when  $X$  is  $-SO_2NR^5R^6$ ,  $R^5$  is hydrogen and  $R^6$  is selected from the group consisting of hydrogen, alkyl and cycloalkyl.

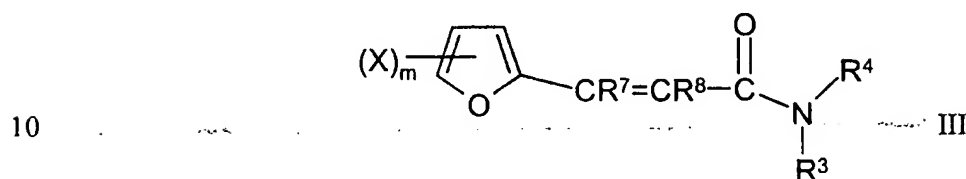
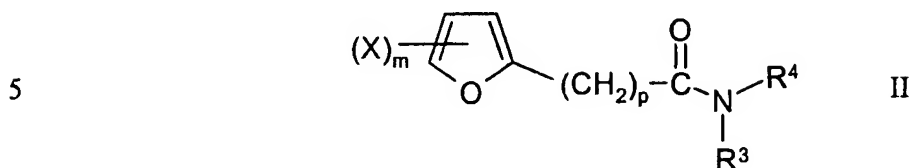
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Preferably,  $m$  in formula I above is 1 or 2. More preferably,  $m$  is 1.



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In another of its composition aspects, this invention is directed to a compound of formula II or III:

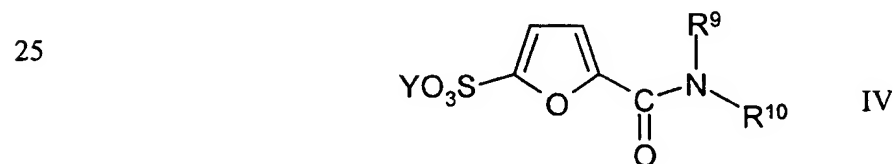


wherein  $R^3$ ,  $R^4$ ,  $X$  and  $m$  are as defined above; and  $R^7$  and  $R^8$  are independently selected from the group consisting of hydrogen and lower alkyl; and  $p$  is an integer from 0 to 6.

15

Preferably, in formula III above,  $R^7$  and  $R^8$  are both hydrogen. In formula II above,  $p$  is preferably 0, 1 or 2. More preferably,  $p$  is 0 or 2.

20 In still another of its composition aspects, this invention is directed to a compound of formula IV:



wherein

30  $R^9$  and  $R^{10}$  are independently selected from the group consisting of hydrogen, lower alkyl and cycloalkyl, provided that  $R^9$  and  $R^{10}$  are not both

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hydrogen; or R<sup>9</sup> and R<sup>10</sup> are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms; and

Y selected from the group consisting of hydrogen and a pharmaceutically acceptable cation.

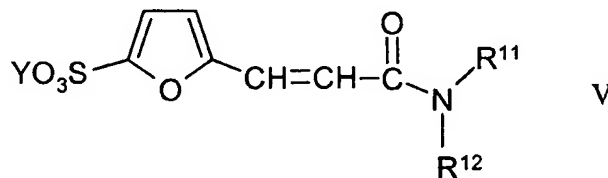
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Preferably, in formula IV above, R<sup>9</sup> is hydrogen and R<sup>10</sup> is isopropyl, *n*-butyl or cyclohexyl. Alternatively, in another preferred embodiment, R<sup>9</sup> and R<sup>10</sup> are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms. Preferably, in formula IV above, Y is hydrogen or a sodium cation.

10

In yet another of its composition aspects, this invention is directed to a compound of formula V:

15



wherein

20

R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of hydrogen, lower alkyl and cycloalkyl, provided that R<sup>11</sup> and R<sup>12</sup> are not both hydrogen; or R<sup>11</sup> and R<sup>12</sup> are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms; and

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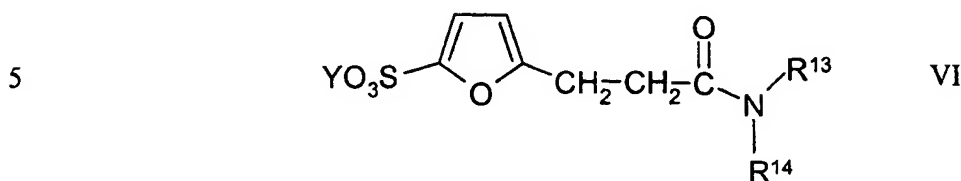
Y selected from the group consisting of hydrogen and a pharmaceutically acceptable cation.

30

Preferably, in formula V above, R<sup>11</sup> is hydrogen and R<sup>12</sup> is isopropyl, *n*-butyl or cyclohexyl. Alternatively, in another preferred embodiment, R<sup>11</sup> and R<sup>12</sup> are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms. Preferably, in formula V above, Y is hydrogen or a sodium cation.

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In still yet another of its composition aspects, this invention is directed to a compound of formula VI:



wherein

10         $R^{13}$  and  $R^{14}$  are independently selected from the group consisting of hydrogen, lower alkyl and cycloalkyl, provided that  $R^{13}$  and  $R^{14}$  are not both hydrogen; or  $R^{13}$  and  $R^{14}$  are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms; and

15        Y selected from the group consisting of hydrogen and a pharmaceutically acceptable cation.

Preferably, in formula VI above,  $R^{13}$  is hydrogen and  $R^{14}$  is isopropyl, *n*-butyl or cyclohexyl. Alternatively, in another preferred embodiment,  $R^{13}$  and  $R^{14}$  are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms.

20        Preferably, in formula VI above, Y is hydrogen or a sodium cation.

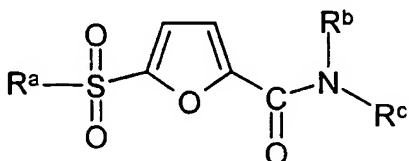
In another of its composition aspects, this invention is directed to a compound selected from the group consisting of:

25        *N*-*n*-butyl-5-carbamoylfuran-2-sulfonic acid  
           *N*-isopropyl-5-carbamoylfuran-2-sulfonic acid  
           *N*-cyclohexyl-5-carbamoylfuran-2-sulfonic acid  
           5-(1-piperidylcarbonyl)furan-2-sulfonic acid  
           5-[2-(*N*-*n*-butylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid  
           5-[2-(*N*-*n*-butylcarbamoyl)ethyl]furan-2-sulfonic acid  
 30        *N*-*n*-butyl-5-(*N*-*n*-butylcarbamoyl)furan-2-sulfonamide  
           *N,N*-diethyl-5-(*N,N*-diethylcarbamoyl)furan-2-sulfonamide,  
           and pharmaceutically acceptable salts thereof.

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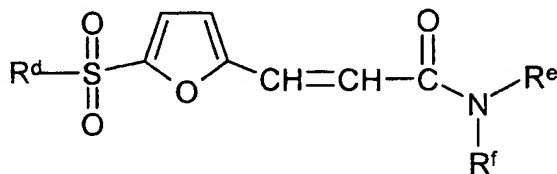
Particularly preferred compounds include those shown in Tables I, II and III and pharmaceutically acceptable salts thereof (i.e., the sodium salts).

Table I



Example No.	R <sup>a</sup>	R <sup>b</sup>	R <sup>c</sup>
1	HO-	H-	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -
2	HO-	H-	(CH <sub>3</sub> ) <sub>2</sub> CH-
3	HO-	H-	cyclohexyl-
4	HO-	R <sup>b</sup> /R <sup>c</sup> = -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -	
7	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> NH-	H-	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -
8	(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> N-	CH <sub>3</sub> CH <sub>2</sub> -	CH <sub>3</sub> CH <sub>2</sub> -

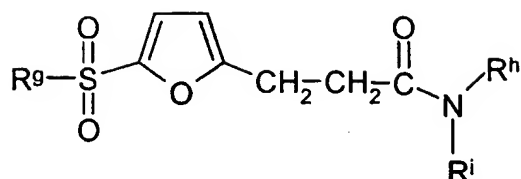
Table II



Example No.	R <sup>d</sup>	R <sup>e</sup>	R <sup>f</sup>
5	HO-	H-	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -

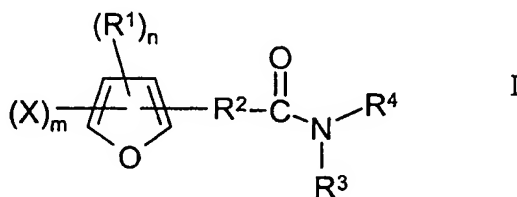
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Table III



Example No.	R <sup>g</sup>	R <sup>h</sup>	R <sup>i</sup>
6	HO-	H-	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -

This invention is also directed to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of formula I:



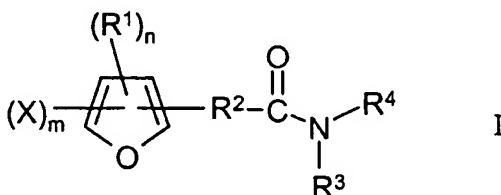
wherein R<sup>1</sup>-R<sup>4</sup>, *n* and *m* are as defined above.

In additional composition aspects, this invention is directed to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of formula II, III, IV, V or VI, which formulae are defined above.

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As previously mentioned, the furansulfonic acid derivatives of this invention have been discovered to inhibit the formation of A $\beta$ (1-40) beta-pleated sheets and/or to protect against A $\beta$ (25-35)-induced neuronal cell loss and/or to reduce  $\beta$ -amyloid-induced release of cytokines, such as IL-1 $\beta$ , IL-6 and TNF $\alpha$ , in human monocyte cells. Such compounds have also been found to reduce the locomotor impairment which results when A $\beta$ (25-35) is injected into the substantia nigra of rats, and the cognitive deficits that develop in certain strains of autoimmune mice. Compounds which have such properties are useful for preventing and/or treating neurodegenerative, autoimmune and inflammatory conditions, such as Alzheimer's disease, multiple sclerosis, lupus, rheumatoid arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS) and the like.

Accordingly, in one of its method aspects, this invention is directed to a method for treating a patient with a neurodegenerative disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective neurodegenerative disease-treating amount of a compound of formula I:

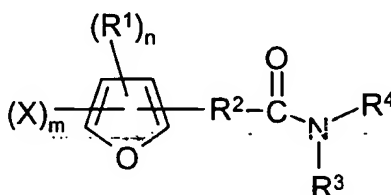


wherein R<sup>1</sup>-R<sup>4</sup>, *n* and *m* are as defined above.

In other method aspects, this invention is directed to methods for treating a patient with a neurodegenerative disease which methods comprise administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective neurodegenerative disease-treating amount of a compound of formula II, III, IV, V or VI, which formulae are defined above.

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In yet another of its method aspects, this invention is directed to a method for preventing the onset of a neurodegenerative disease in a patient at risk for developing the neurodegenerative disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective neurodegenerative disease-preventing amount of a compound of formula I:



wherein  $R^1$ - $R^4$ ,  $n$  and  $m$  are as defined above.

In still other method aspects, this invention is directed to methods for preventing the onset of a neurodegenerative disease in a patient at risk for developing the neurodegenerative disease which methods comprise administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective neurodegenerative disease-preventing amount of a compound of formula II, III, IV, V or VI, which formulae are defined above.

In another of its method aspects, this invention is directed to methods for treating a patient with an autoimmune disease which methods comprise administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective autoimmune disease-treating amount of a compound of formula I, II, III, IV, V or VI, which formulae are defined above.

In yet another of its method aspects, this invention is directed to a method for preventing the onset of an autoimmune disease in a patient at risk for developing the autoimmune disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable

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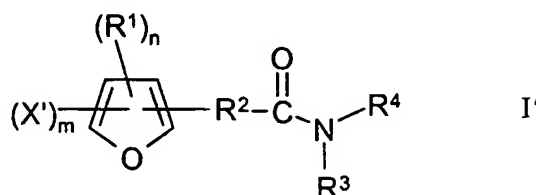
carrier and an effective autoimmune disease-preventing amount of a compound of formula I, II, III, IV, V or VI, which formulae are defined above.

In still another of its method aspects, this invention is directed to methods for treating a patient with an inflammatory disease which methods comprise administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective inflammatory disease-treating amount of a compound of formula I, II, III, IV, V or VI, which formulae are defined above.

In yet another of its method aspects, this invention is directed to a method for preventing the onset of an inflammatory disease in a patient at risk for developing the inflammatory disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective inflammatory disease-preventing amount of a compound of formula I, II, III, IV, V or VI, which formulae are defined above.

In another of its aspects, this invention is directed to the use of a compound of formula I, II, III, IV, V or VI in the manufacture of a formulation or medicament for a medicinal treatment. Preferably, the medical treatment is the therapeutic or prophylactic treatment of a neurodegenerative disease, an autoimmune disease or an inflammatory disease.

And, in still another of its method aspects, this invention is directed to a process for preparing a carbamoyl-substituted furansulfonic acid of formula I':



wherein



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each  $R^1$  is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

5  $R^2$  is selected from the group consisting of alkylene, alkenylene and a covalent bond;

$R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that  $R^3$  and  $R^4$  are not both hydrogen; or  $R^3$  and  $R^4$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a  
10 heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

each  $X'$  is  $-SO_3Y$ , wherein  $Y$  is hydrogen or a pharmaceutically acceptable cation;

$m$  is an integer from 1 to 3; and  $n$  is an integer from 0 to 2, provided that  $m$   
15  $+ n = 3$ ; said process comprising the steps of:

(a) reacting a furan carboxylic acid halide of the formula:

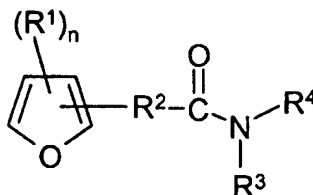


wherein  $R^1$ ,  $R^2$  and  $n$  are as defined above and  $W$  is chloro or bromo, with an amine of the formula:



wherein  $R^3$  and  $R^4$  are as defined above, to provide a furan carboxamide of the  
30 formula:

-- 15 --



5

and

(b) reacting the furan carboxamide with a sulfonating reagent to provide the carbamoyl-substituted furan sulfonic acid.

10

Preferably, the sulfonating reagent employed in this process is sulfur trioxide pyridine complex.

15

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a bar graph illustrating the acquisition scores for MRL wild-type mice ("++") treated with 1% methylcellulose ("MC"), and Fas<sup>lpr</sup> mutant strains of mice treated with 1% methylcellulose or 100 mg/kg of *N*-*n*-butyl-5-carbamoylfuran-2-sulfonic acid sodium salt ("Compound 1").

20

Figure 2 is a bar graph illustrating the avoidance scores for wild-type mice ("++") treated with 1% methylcellulose ("MC"), and Fas<sup>lpr</sup> strains of mice treated with 1% methylcellulose or 100 mg/kg of *N*-*n*-butyl-5-carbamoylfuran-2-sulfonic acid sodium salt ("Compound 1").

25

#### DETAILED DESCRIPTION OF THE INVENTION

As discussed above, the furansulfonic acid derivatives of this invention are useful for preventing and/or treating neurodegenerative, autoimmune and inflammatory conditions in mammals. When describing such compounds or pharmaceutical compositions containing such compounds or methods of using

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such compounds, the following terms have the following meanings unless otherwise indicated.

### Definitions

5           The term "β-amyloid peptide" refers to a 39-43 amino acid peptide having a molecular weight of about 4.2 kD, which peptide is substantially homologous to the form of the peptide described by Glenner, et al., *Biochem. Biophys. Res. Commun.*, 120:885-890 (1984), including mutations and post-translational modifications of the normal β-amyloid peptide.

10

          The term "cytokines" refers to peptide or protein mediators that are produced by immune cells to modulate cellular functions. Examples of cytokines include, interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα).

15

          "Alkyl" refers to monovalent alkyl groups preferably having from 1 to about 12 carbon atoms, more preferably 1 to 8 carbon atoms and still more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-hexyl, *n*-octyl, 20 *tert*-octyl and the like. The term "lower alkyl" refers to alkyl groups having 1 to 6 carbon atoms.

          "Alkylene" refers to divalent alkylene groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms which can be straight 25 chain or branched. This term is exemplified by groups such as methylene (-CH<sub>2</sub>-), ethylene (-CH<sub>2</sub>CH<sub>2</sub>-), the propylene isomers (e.g., -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and -CH(CH<sub>3</sub>)CH<sub>2</sub>-) and the like.

          "Alkenylene" refers to divalent alkenylene groups preferably having from 2 30 to 10 carbon atoms and more preferably 2 to 6 carbon atoms which can be straight chain or branched and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-),

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the propenylene isomers (e.g.,  $-\text{CH}=\text{CHCH}_2-$  and  $-\text{C}(\text{CH}_3)=\text{CH}-$  and  $-\text{CH}=\text{C}(\text{CH}_3)-$ ) and the like.

5 "Alkaryl" refers to -alkylene-aryl groups preferably having from 1 to 10 carbon atoms in the alkylene moiety and from 6 to 14 carbon atoms in the aryl moiety. Such alkaryl groups are exemplified by benzyl, phenethyl, and the like.

10 "Alkcycloalkyl" refers to -alkylene-cycloalkyl groups preferably having from 1 to 10 carbon atoms in the alkylene moiety and from 3 to 8 carbon atoms in the cycloalkyl moiety. Such alkcycloalkyl groups are exemplified by  $-\text{CH}_2$ -cyclopropyl,  $-\text{CH}_2$ -cyclopentyl,  $-\text{CH}_2\text{CH}_2$ -cyclohexyl, and the like.

15 "Alkoxy" refers to the group "alkyl-O-". Preferred alkoxy groups include, by way of example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

"Alkoxy carbonyl" refers to the group  $-\text{C}(\text{O})\text{OR}$  where R is alkyl.

20 "Alkenyl" refers to alkenyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. Preferred alkenyl groups include ethenyl ( $-\text{CH}=\text{CH}_2$ ), *n*-propenyl ( $-\text{CH}_2\text{CH}=\text{CH}_2$ ), isopropenyl ( $-\text{C}(\text{CH}_3)=\text{CH}_2$ ), and the like.

25 "Alkynyl" refers to alkynyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation. Preferred alkynyl groups include ethynyl ( $-\text{C}\equiv\text{CH}$ ), propargyl ( $-\text{CH}_2\text{C}\equiv\text{CH}$ ), and the like.

30 "Aminocarbonyl" refers to the group  $-\text{C}(\text{O})\text{NRR}$  where each R is independently hydrogen or alkyl.

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"Aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen or alkyl.

5 "Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like. Unless otherwise constrained by the definition for the individual substituent, such aryl groups can optionally be substituted with from 1 to 3 substituents selected from the group consisting of alkyl, alkoxy, alkenyl, alkynyl, amino, aminoacyl, 10 aminocarbonyl, alkoxycarbonyl, aryl, carboxyl, cyano, halo, hydroxy, nitro, trihalomethyl and the like.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed rings which can be optionally 15 substituted with from 1 to 3 alkyl groups. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

20 "Cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 10 carbon atoms having a single cyclic ring and at least one point of internal unsaturation which can be optionally substituted with from 1 to 3 alkyl groups. Examples of suitable cycloalkenyl groups include, for instance, cyclopent-3-enyl, cyclohex-2-enyl, cyclooct-3-enyl and the like.

25

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo. Preferred halo groups are either fluoro or chloro.

30 "Heterocycle" or "heterocyclic" refers to a monovalent saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur or

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oxygen within the ring. Examples of heterocycles include, but are not limited to, morpholine, piperazine, imidazolidine and the like.

5 "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts which are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the  
10 like. The term "pharmaceutically acceptable cation" refers to a pharmaceutically acceptable cationic counterion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

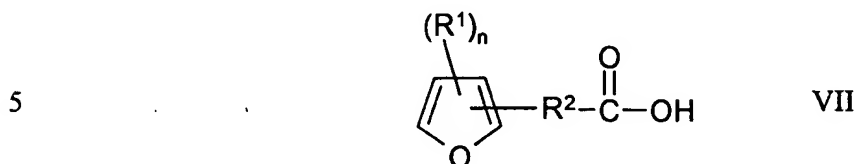
#### 15 General Synthetic Procedures

The furansulfonic acid derivatives of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents,  
20 pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

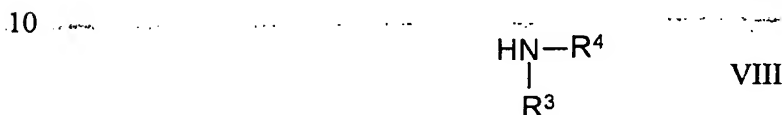
25 Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups,  
30 and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

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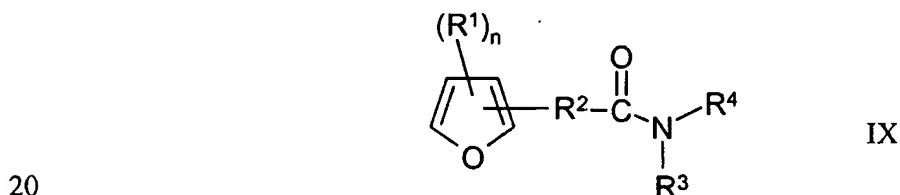
In a preferred method of synthesis, the furansulfonic acid derivatives of this invention are prepared by first coupling a furan carboxylic acid of formula VII:



wherein R<sup>1</sup>, R<sup>2</sup> and *n* are as defined above, with an amine of formula VIII:



wherein R<sup>3</sup> and R<sup>4</sup> are as defined above, to provide a furan carboxamide of formula IX:



wherein R<sup>1</sup>-R<sup>4</sup> and *n* are as defined above.

25 The furan carboxylic acids of formula VII are either known compounds or can be prepared from known compounds by conventional procedures. Preferred furan carboxylic acid starting materials include 2-furoic acid (furan-2-carboxylic acid), 3-furoic acid, 3-(furan-2-yl)propionic acid, 3-(furan-3-yl)propionic acid, 3-(furan-2-yl)prop-2-enoic acid, 3-(furan-3-yl)prop-2-enoic acid and the like.

30 The amines of formula VIII are also known compounds or compounds that can be prepared from known compounds by conventional procedures. Preferred amines for use in this invention include methylamine, ethylamine, *n*-propylamine,

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isopropylamine, *n*-butylamine, isobutylamine, *sec*-butylamine, *tert*-butylamine, *n*-pentylamine, cyclopentylamine, *n*-hexylamine, cyclohexylamine, *n*-octylamine, *tert*-octylamine, dimethylamine, diethylamine, di-*n*-propylamine, -  
diisopropylamine, di-*n*-butylamine, diisobutylamine, di-*sec*-butylamine, di-*n*-  
5 hexylamine, methylethylamine, methyl-*n*-propylamine, methylisopropylamine, -  
methyl-*n*-butylamine, methyl-*tert*-butylamine, methyl-*tert*-octylamine, methyl-  
cyclopentylamine, methylcyclohexylamine, ethyl-*n*-propylamine,  
ethylisopropylamine, ethyl-*n*-butylamine, ethylcyclohexylamine, phenylamine, (4-  
methyl)phenylamine, pyrrolidine, piperidine, morpholine and the like.  
10 Especially preferred amines include, isopropylamine, *n*-butylamine,  
cyclohexylamine, diethylamine and piperidine.

The coupling reaction of furan carboxylic acid VII with amine VIII can be  
conducted using any conventional coupling reagent including, for example,  
15 carbodiimides such as dicyclohexylcarbodiimide and other promoting agents, such  
as *N,N'*-carbonyldiimidazole. This reaction can be conducted with or without the  
use of well known additives such as *N*-hydroxysuccinimide, 1-  
hydroxybenzotriazole, etc. which are known to facilitate the coupling of carboxylic  
acids and amines.

20 Alternatively, in a preferred embodiment, the acid halide of compound VII  
can be employed in the coupling reaction. The acid halide of VII can be prepared  
by contacting VII with an inorganic acid halide, such as thionyl chloride,  
phosphorous trichloride, phosphorous tribromide or phosphorous pentachloride, or  
25 alternatively, with oxalyl chloride under conventional conditions. Generally, this  
reaction is conducted using about 1 to 5 molar equivalents of the inorganic acid  
halide or oxalyl chloride, either neat or in an inert solvent, such as carbon  
tetrachloride, at temperature in the range of about 0°C to about 80°C for about 1 to  
about 48 hours. A catalyst, such as *N,N*-dimethylformamide, may also be used in  
30 this reaction.



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When an acyl halide is employed in the coupling reaction, it is typically reacted with amine VIII in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like.

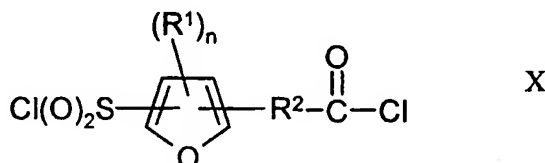
5 Alternatively, an excess of amine VIII may be used to scavenge the acid generated during the reaction.

The coupling reaction using either furan carboxylic acid VII or its acid halide is preferably conducted at a temperature of from about 0°C to about 60°C for about 1 to about 24 hours. Typically, the reaction is conducted in an inert aprotic polar solvent such as dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like using about 1 to about 5 molar equivalents of the amine based on the furan carboxylic acid or its acid halide. Upon completion of the reaction, the furan carboxamide IX is recovered by  
15 conventional methods including precipitation, chromatography, filtration, distillation and the like.

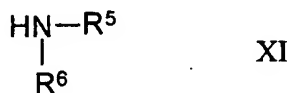
The furan carboxamide IX is then sulfonated using conventional sulfonating reagents to provide furansulfonic acid derivatives of formula I above, wherein X is -SO<sub>3</sub>Y and Y is as defined above. A preferred sulfonating reagent for use in this  
20 reaction is sulfur trioxide pyridine complex. Typically, the sulfonation reaction is conducted by contacting the furan carboxamide IX with about 1 to about 5 molar equivalent of the sulfonating reagent in an inert solvent, such as 1,2-dichloroethane, at a temperature ranging from about 50°C to about 200°C, preferably at about 100°C to about 150°C, for about 6 to about 48 hours. Upon  
25 completion of the reaction, the furansulfonic acid compound is recovered by conventional methods including precipitation, chromatography, filtration and the like. Surprisingly, the yield for this sulfonation reaction is significantly higher than that obtained for sulfonation of the corresponding furan carboxylic acid VII  
30 under similar conditions.

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The furan sulfonamide derivatives of formula I, i.e., those compounds wherein X is  $-\text{SO}_2\text{NR}^5\text{R}^6$  where  $\text{R}^5$  and  $\text{R}^6$  are as defined above, are readily prepared from the corresponding chlorocarbonylfuran sulfonyl chloride of formula X:



10 wherein  $\text{R}^1$ ,  $\text{R}^2$  and  $n$  are as defined above, by reaction with an amine of formula XI:



wherein  $\text{R}^5$  and  $\text{R}^6$  are as defined above, under conventional reaction conditions.

The amines of formula XI are either known compounds or compounds that can be prepared by known procedures. Examples of suitable amines for use in this reaction include, but are not limited to, methylamine, ethylamine, *n*-propylamine, isopropylamine, *n*-butylamine, isobutylamine, *sec*-butylamine, *tert*-butylamine, *n*-pentylamine, cyclopentylamine, *n*-hexylamine, cyclohexylamine, *n*-octylamine, *tert*-octylamine, dimethylamine, diethylamine, di-*n*-propylamine, -

20 diisopropylamine, di-*n*-butylamine, diisobutylamine, di-*sec*-butylamine, di-*n*-hexylamine, methylethylamine, methyl-*n*-propylamine, methylisopropylamine, - methyl-*n*-butylamine, methyl-*tert*-butylamine, methyl-*tert*-octylamine, methyl-cyclopentylamine, methylcyclohexylamine, ethyl-*n*-propylamine, ethylisopropylamine, ethyl-*n*-butylamine, ethylcyclohexylamine, phenylamine, (4-

25 methyl)phenylamine, pyrrolidine, piperidine, morpholine and the like.

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The chlorocarbonylfuran sulfonyl chlorides of formula X are also known compounds or compounds which can be prepared from known compounds by conventional procedures. Typically, these compounds are prepared from the corresponding carboxyfuran sulfonic acid by treatment with phosphorous oxychloride and phosphorous pentachloride. This reaction is generally conducted by contacting the carboxyfuran sulfonic acid with about 2 to about 10 equivalents of phosphorous oxychloride and about 2 to about 5 equivalents of phosphorous pentachloride at a temperature ranging from about 0°C to about 30° for about 1 to 12 hours. The carboxyfuran sulfonic acids employed in this reaction are either known compounds or compounds which can be prepared from known compounds by conventional procedures. For example, carboxyfuran sulfonic acids can be prepared from the corresponding formylfuran sulfonic acids by oxidation using conventional oxidizing agents, such as potassium dichromate.

The sulfonamide derivatives of formula I in which  $R^5 = R^3$  and  $R^6 = R^4$ , i.e., those compounds in which the carboxamide and sulfonamide groups are derived from the same amine, are readily prepared by contacting the sulfonyl chloride X with an excess of amine XI, preferably with about 2 to about 5 equivalents of amine XI. Typically, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, an excess of amine XI may be used to scavenge the acid generated during the reaction.

Reaction of the sulfonyl chloride X with amine XI is preferably conducted at a temperature ranging from about 0°C to about 60°C for about 1 to about 24 hours. Upon completion of the reaction, the resulting carbamoylfuran sulfonamide is recovered by conventional methods including precipitation, chromatography, filtration, and the like.

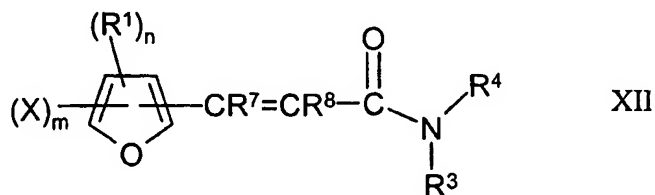
The sulfonamide derivatives of formula I in which  $R^5 \neq R^3$  and/or  $R^6 \neq R^4$ , i.e., those compounds in which the carboxamide and sulfonamide groups are

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derived from different amines, can be prepared by first selectively reacting the chlorocarbonylfuran sulfonyl chloride with an alcohol, such as methanol or ethanol, under conventional conditions to form the corresponding alkoxy carbonylfuran sulfonyl chloride. See, for example, L. S. Abovyan et al., *Khim.-Farm. Zh.* (1983), 17(6) 685-688. The alkoxy carbonylfuran sulfonyl chloride is then reacted with about 1 to about 5 equivalents of amine XI to afford the corresponding alkoxy carbonylfuran sulfonamide. This reaction is preferably conducted at a temperature ranging from about 0°C to about 60°C for about 1 to about 24 hours in the presence of a suitable base, such as triethylamine, to scavenge the acid generated during the reaction. Alternatively, an excess of amine XI may be used to scavenge the acid generated during the reaction.

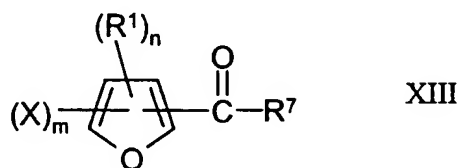
The ester group of the alkoxy carbonylfuran sulfonamide is then hydrolyzed under conventional conditions to form the corresponding carboxyfuran sulfonamide. This reaction is typically conducted by contacting the alkoxy carbonylfuran sulfonamide with about 1 to about 1.2 equivalents of an alkali metal hydroxide, such as lithium hydroxide, sodium hydroxide or potassium hydroxide, in a suitable solvent, such as tetrahydrofuran/water or dioxane/water, at a temperature ranging from about 0°C to about 25°C for about 1 to 24 hours. The resulting carboxyfuran sulfonamide can then be coupled to amine IV using the procedures described above to provide the corresponding carbamoylfuran sulfonamide of formula I.

Alternatively, in another preferred method of synthesis, the furansulfonic acid derivatives of this invention having formula XII:

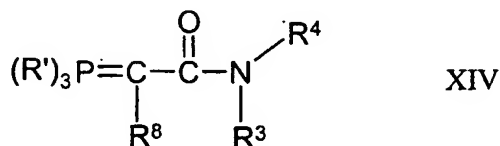


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wherein  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^7$ ,  $R^8$ ,  $X$ ,  $m$  and  $n$  are as defined above, can be prepared by reacting a furan carbonyl compound of formula XIII:



wherein  $R^1$ ,  $R^7$ ,  $X$ ,  $m$  and  $n$  are as defined above, with a Wittig reagent of formula XIV:



15

wherein  $R^3$ ,  $R^4$  and  $R^8$  are as defined above, and each  $R'$  is preferably aryl, such as phenyl, or two of  $R'$  are preferably alkyl, such as methyl, ethyl and the like, and the remaining  $R'$  is =O.

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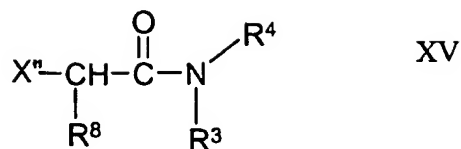
The furan carbonyl compounds of formula XIII are either known compounds or compounds that can be prepared from known compounds by conventional procedures. Preferred furan carbonyl compounds for use in this invention include, but are not limited to, 5-formylfuran-2-sulfonic acid, 4-formylfuran-2-sulfonic acid, 3-formylfuran-2-sulfonic acid, 5-acetylfuran-2-sulfonic acid and the like.

25

The Wittig reagents of formula XIV are also known compounds or compounds that can be prepared from known compounds by conventional procedures. Typically, the Wittig reagent is prepared by first contacting a triaryl phosphine, such as triphenylphosphine, or a trialkyl phosphite, such as trimethyl phosphite or triethyl phosphite, with an  $\alpha$ -halo carboxamide of formula XV:

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wherein  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^8$  are as defined above, and  $\text{X}''$  is chloro, bromo or iodo, to form a triarylphosphonium salt or a phosphonate ester. This reaction is typically conducted in an inert solvent, such as toluene and the like, at a temperature ranging from about  $50^\circ\text{C}$  to about  $150^\circ\text{C}$  for about 24 to about 48 hours. The Wittig reagent XIV is then formed by treatment of the triarylphosphonium salt or the phosphonate ester with at least one molar equivalent of a strong base, such as *n*-butyl lithium and the like. Preferably, the Wittig reagent XIV is generated *in situ* just prior to reaction with the furan carbonyl compound XIII.

15

The Wittig reaction is typically conducted by contacting the furan carbonyl compound XIII with about 1 to about 2 molar equivalents of the Wittig reagent XIV. When the X group in formula XIII above is  $-\text{SO}_3\text{H}$ , the sulfonate group is generally converted to a suitable salt, such as the sodium or lithium salt, by treatment with a base, such as sodium hydride, prior to reaction with the Wittig reagent. The Wittig reaction is typically conducted at a temperature ranging from about  $-20^\circ\text{C}$  to about  $80^\circ\text{C}$ , preferably about  $0^\circ$  to about  $5^\circ\text{C}$ , for about 1 to about 24 hours in an inert solvent, such as tetrahydrofuran. Upon completion of the reaction, the furansulfonic acid of formula XIII is recovered by conventional methods including precipitation, chromatography, filtration, and the like.

25

Additionally, in a further preferred method of synthesis, the furansulfonic acid derivatives of formula XII above can be hydrogenated using conventional reagents and conditions to provide for compounds in which the unsaturation between the furan ring and the amide group has been saturated. This reaction is typically conducted by hydrogenating a compound of formula XII under about 1 to about 4 atmospheres of hydrogen in the presence of catalyst, such as palladium on carbon. Generally, this reaction is conducted in an inert solvent, such as ethanol,

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at a temperature ranging from about 10°C to about 60°C for about 1 to about 48 hours. Upon completion of the reaction, the product is recovered by conventional methods including extraction, precipitation, chromatography, filtration, and the like.

5

#### Pharmaceutical Compositions

When employed as pharmaceuticals, the furansulfonic acid derivatives of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

10

Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

15

The pharmaceutical compositions of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds of this invention are preferably formulated as either injectable or oral compositions.

20

The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid

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compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the furansulfonic acid compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and  
5 processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the  
10 following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as  
15 peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the furansulfonic acid compound in such compositions is typically a minor  
20 component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

The above described components for orally administrable or injectable compositions are merely representative. Other materials as well as processing  
25 techniques and the like are set forth in Part 8 of Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

The compounds of this invention can also be administered in sustained  
30 release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in the incorporated materials in Remington's Pharmaceutical Sciences.



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The following formulation examples illustrate representative pharmaceutical compositions of this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

5     Formulation 1 - Tablets

A compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active furansulfonic acid compound per tablet) in a tablet press.

10

Formulation 2 - Capsules

A compound of formula I is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active furansulfonic acid compound per capsule).

15

Formulation 3 - Liquid

A compound of formula I (125 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total volume of 5 mL.

20

25     Formulation 4 - Tablets

The compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active furansulfonic acid compound) in a tablet press.

30

Formulation 5 - Injection

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The compound of formula I is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

#### Compound Utility

5           The furansulfonic acid derivatives of this invention have been discovered to inhibit the formation of A $\beta$ (1-40) beta-pleated sheets and/or protect against neuronal cell loss and/or inhibit the release of cytokines, such as IL-1 $\beta$ , IL-6 and TNF $\alpha$ . Additionally, such compounds have been found to reduce the locomotor impairment caused by A $\beta$ (25-35) and to reduce the cognitive deficits in certain  
10       autoimmune strains of mice. As previously discussed, the formation of A $\beta$ (1-40) beta-pleated sheets, neuronal cell loss and cognitive deficits are associated with neurodegenerative conditions, such as Alzheimer's disease, and/or autoimmune conditions. Additionally, elevated levels of cytokines are associated with neurodegenerative, autoimmune and/or inflammatory conditions. Accordingly, the  
15       compounds and pharmaceutical compositions of this invention find use as therapeutics for preventing and/or treating neurodegenerative, autoimmune and inflammatory conditions in mammals including humans.

          Among the conditions which may be treated and/or prevented with the  
20       furansulfonic acid derivatives of formula I are neurodegenerative conditions, such as Alzheimer's disease, Parkinson's disease, HIV-dementia and the like; autoimmune conditions, such as systemic lupus (erythematosus) and the like; and inflammatory conditions, such as inflammatory bowel disease, rheumatoid arthritis, septic shock, erythema nodosum leprosy, septicemia, uveitis, adult  
25       respiratory distress syndrome (ARDS), multiple sclerosis and the like.

          Additionally, the furansulfonic acid derivatives of this invention have been discovered to effectively inhibit the release of cytokines, such as IL-1 $\beta$ , IL-6 and TNF $\alpha$ . Elevated levels of certain cytokines are associated with a wide variety of  
30       inflammatory neurodegenerative and autoimmune conditions, including Alzheimer's disease, AIDS dementia, septic shock, rheumatoid arthritis, erythema nodosum leprosy, meningococcal meningitis, multiple sclerosis, systemic lupus

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and the like. See, L. Sekut et al., *Drug News Perspect.* **1996**, *9*, 261; K. Shiosaki et al., "Chapter 4. Emerging Opportunities in Neuroinflammatory Mechanisms of Neurodegeneration" *Annual Reports in Medicinal Chemistry*, pp. 31-40, Academic Press (1995) and reference cited therein; and A. Waage et al., *J. Exp. Med.* **1989**, *170*, 1859-1867. Accordingly, the furansulfonic acid derivatives of formula I are  
5 useful for treating diseases characterized by an overproduction or an unregulated production of cytokines, particularly IL-1 $\beta$ , IL-6 and TNF $\alpha$ , including neurodegenerative, autoimmune and/or inflammatory conditions.

10 As discussed above, the compounds described herein are suitable for use in a variety of drug delivery systems. Injection dose levels for treating neurodegenerative, autoimmune and inflammatory conditions range from about 0.1 mg/kg/hour to at least 10 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. A preloading bolus of from about 0.1 mg/kg to about 10  
15 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

For the prevention and/or treatment of long-term conditions, such as  
20 neurodegenerative and autoimmune conditions, the regimen for treatment usually stretches over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.1 to about 20 mg/kg of  
25 furansulfonic acid derivative, with preferred doses each providing from about 0.1 to about 10 mg/kg and especially about 1 to about 5 mg/kg.

When used to prevent the onset of a neurodegenerative, autoimmune or inflammatory condition, the furansulfonic acid derivatives of this invention will be  
30 administered to a patient at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Patients at risk for developing a particular condition generally include

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those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

5           The compounds of this invention can be administered as the sole active agent or they can be administered in combination with other agents, including other active furansulfonic acid derivatives.

          The following synthetic and biological examples are offered to illustrate  
10       this invention and are not to be construed in any way as limiting the scope of this invention.

### EXAMPLES

          In the examples below, the following abbreviations have the following  
15       meanings. Abbreviations not defined below have their generally accepted meaning.

	bd	=	broad doublet
	bs	=	broad singlet
	d	=	doublet
20	dd	=	doublet of doublets
	dec	=	decomposed
	dH <sub>2</sub> O	=	distilled water
	DIV	=	days <i>in vitro</i>
	ELISA	=	enzyme-linked immuno-sorbent assay
25	EtOAc	=	ethyl acetate
	EtOH	=	ethanol
	FBS	=	fetal bovine serum
	g	=	grams
	h	=	hours
30	Hz	=	hertz
	IL-1 $\beta$	=	interleukin-1 $\beta$
	IL-6	=	interleukin-6
	L	=	liter
	LPS	=	lipopolysaccharide
35	m	=	multiplet
	min	=	minutes
	M	=	molar
	MeOH	=	methanol
	mg	=	milligram

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	MHz	=	megahertz
	mL	=	milliliter
	mmol	=	millimole
	m.p.	=	melting point
5	N	=	normal
	q	=	quartet
	quint.	=	quintet
	s	=	singlet
	t	=	triplet
10	THF	=	tetrahydrofuran
	ThT	=	thioflavin T
	tlc	=	thin layer chromatography
	TNF $\alpha$	=	tumor necrosis factor- $\alpha$
	$\mu$ g	=	microgram
15	$\mu$ L	=	microliter
	UV	=	ultraviolet

In the examples below, all temperatures are in degrees Celsius (unless otherwise indicated). Examples A and B describe the synthesis of various intermediates used to prepare the furansulfonic acid derivatives of this invention; Examples 1-8 describe the synthesis of furansulfonic acid derivatives; and Examples 9-13 describe the *in vitro* and *in vivo* testing of such compounds.

#### 25 Example A

##### Synthesis of *N-n*-Butylfuran-2-carboxamide

To a solution of *n*-butylamine (99 mL, 1.0 mol) in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) was added 2-furoyl chloride (33.0 mL, 0.335 mol) dropwise at 0-5°C with stirring.

30 The reaction mixture was stirred for additional 2 h at 0-5°C and overnight at room temperature. The solution was poured into a mixture of wet-ice (200 g) and 37% HCl (50 mL). After separation, the organic layer was washed with 2 x 200 mL water, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. Removal of solvent provided the title compound (49.59 g, 88.6% yield) as a white solid, m.p. = 43.8°C (R<sub>f</sub> = 0.53 on a

35 silica gel plate using EtOAc as an eluant). This product was used without further purification.

Spectroscopic data were as follows:

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IR (KBr,  $\text{cm}^{-1}$ ): 3314 (NH), 3122 (furan CH), 2959.2 (CH), 2932.9 (CH), 2872.7 (CH), 1646.5 (C=O), 1595.2 (furan ring), 1535.0 (NH), 1307.2 (C-N).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz):  $\delta$  = 7.357 (1H, dd,  $J_1$  = 1.7 Hz,  $J_2$  = 0.7 Hz, furan CH), 7.027 (1H, dd,  $J_1$  = 3.5 Hz,  $J_2$  = 0.7 Hz, furan CH), 6.416 (1H, dd,  $J_1$  = 3.5 Hz,  $J_2$  = 1.7 Hz, furan CH), 6.453 (1H, broad s, NH), 3.359 (2H, m,  $\text{CH}_2$ ), 1.522 (2H, m,  $\text{CH}_2$ ), 1.364 (2H, m,  $\text{CH}_2$ ), and 0.881 (3H, t,  $J$  = 7.3 Hz,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 270 MHz):  $\delta$  = 158.779, 148.529, 143.937, 113.888, 112.104, 38.552, 31.398, 19.653, and 13.277.

10

### Example B

#### Synthesis of (*N-n*-Butylcarbamoyl)methyltriphenylphosphonium Chloride

A solution of triphenyl phosphine (26.23 g, 0.1 mol) and *n*-butyl chloroacetamide (14.96 g, 0.1 mol) in toluene (250 mL) was refluxed with stirring for 22 h. After cooling to room temperature, the mixture was filtered and dried under high vacuum to afford 36.72 g (89.1% yield) of the title compound as white crystals. This material was used without further purification.

15

Spectroscopic data were as follows:

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 270 MHz):  $\delta$  = 9.209 (1H, t,  $J$  = 5.5 Hz, NH), 7.786 (15H, m, 3  $\text{C}_6\text{H}_5$ ), 5.141 (2H, d,  $J_p$  = 15.3 Hz,  $\text{PCH}_2$ ), 2.912 (2H, m,  $\text{NCH}_2$ ), 1.127 (4H, m,  $\text{CH}_2\text{CH}_2$ ), and 0.752 (3H, t,  $J$  = 7.2 Hz,  $\text{CH}_3$ ).

20

### Example 1

#### Synthesis of *N-n*-Butyl-5-carbamoylfuran-2-sulfonic Acid Sodium Salt

25

Sulfur trioxide pyridine complex (38.07 g, 239.22 mmol) and 1,2-dichloroethane (200 mL) were mixed with *N-n*-butylfuran-2-carboxamide (20 g, 119.61 mmol), from Example A above, in a Parr pressure reactor. The reactor was sealed and heated to 140°C. After 22 h at 140°C, the reactor was cooled to room temperature and the mixture was concentrated on a rotary evaporator to give a dark slurry. The residue was treated with a solution of  $\text{Na}_2\text{CO}_3$  (27.8 g, 262 mmol) in water (200 mL) and the resulting mixture was evaporated to dryness. The

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resulting solid was stirred with methylene chloride (300 mL) to remove unreacted starting material and the undissolved brown solid was refluxed with ethanol (500 mL) for 30 min and then filtered. The filtrate was concentrated on a rotary evaporator to provide 25.95 grams of a solid. The solid was then dissolved in water and the resulting aqueous solution was treated with charcoal and filtered through a short column of silica gel, eluting with water (150 mL). Removal of the water afforded the sodium salt of the title compound (21.95 grams, 68.1% yield) as slightly yellowish solid, m.p. = 223.6°C ( $R_f$  = 0.47 on a silica gel plate using 2:1 EtOAc/EtOH).

10 Spectroscopic data were as follows:

IR (KBr,  $\text{cm}^{-1}$ ): 3440.5 (broad, hydrate & NH), 2960.3 (CH), 2934.3 (CH), 2873.2 (CH), 1650.2 (C=O), 1598.0 (furan ring), 1547.0 (NH), 1307.2 (C-N), 1246 ( $\text{SO}_2$ ), 1221.7 ( $\text{SO}_2$ ), and 1052.7 ( $\text{SO}_3$ ).

$^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 270 MHz):  $\delta$  = 7.106 (1H, d,  $J$ =3.7 Hz, furan CH), 6.923 (1H, d,  $J$ =3.7 Hz, furan CH), 3.326 (2H, t,  $J$ =6.9 Hz,  $\text{CH}_2\text{N}$ ), 1.533 (2H, m,  $\text{CH}_2$ ), 1.329 (2H, m,  $\text{CH}_2$ ), and 0.869 (3H, t,  $J$ =7.3 Hz,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 270 MHz):  $\delta$  = 160.182, 153.562, 147.918, 115.154, 113.232, 39.010, 30.346, 19.165, and 12.698.

20

## Example 2

### Synthesis of

#### *N*-Isopropyl-5-carbamoylfuran-2-sulfonic Acid Sodium Salt

The title compound was prepared from *N*-isopropylfuran-2-carboxamide and sulfur trioxide pyridine complex using the procedure described in Example 1 above. The title compound was isolated in 36.7% yield as a solid, m.p. = 237.2°C ( $R_f$  = 0.47 on a silica gel plate using 3:1 EtOAc/EtOH).

25 Spectroscopic data were as follows:

IR (KBr,  $\text{cm}^{-1}$ ): 3305.4 (NH), 2970.8 (CH), 1659.5 (C=O), 1597.5 (furan ring), 1544.2 (NH), 1249.9 ( $\text{SO}_2$ ), 1203.8 ( $\text{SO}_2$ ), and 1049.8 ( $\text{SO}_3$ ).

30  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 270 MHz):  $\delta$  = 7.121 (1H, d,  $J$ =3.6 Hz, furan CH), 6.936 (1H, d,  $J$ =3.6 Hz, furan CH), 4.105 (1H, septet,  $J$ =6.6 Hz, CH), and 1.224 (6H, d,  $J$ =6.6 Hz, 2  $\text{CH}_3$ ).

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$^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 270 MHz):  $\delta$  = 159.313, 153.577, 147.964, 115.169, 113.171, 41.999, and 21.117.

### Example 3

5

#### Synthesis of

#### *N*-Cyclohexyl-5-carbamoylfuran-2-sulfonic Acid Sodium Salt

The title compound was prepared from *N*-cyclohexylfuran-2-carboxamide and sulfur trioxide pyridine complex using the procedure described in Example 1 above. The title compound was isolated in 75.3% yield as a solid, m.p. = 242.5°C (dec) ( $R_f$  = 0.45 on a silica gel plate using 2:1 EtOAc/EtOH).

10

Spectroscopic data were as follows:

IR (KBr,  $\text{cm}^{-1}$ ): 3258.0 (NH), 2933.3 (CH), 1641.1 (C=O), 1579.3 (furan ring), 1545.6 (NH), 1240.0 ( $\text{SO}_2$ ), 1219.0 ( $\text{SO}_2$ ), and 1049.1 ( $\text{SO}_3$ ).

15

$^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 270 MHz):  $\delta$  = 7.141 (1H, d,  $J$ =3.7 Hz, furan CH), 6.943 (1H, d,  $J$ =3.7 Hz), 3.747 (1H, m, CHN), 1.880 (2H, m, cyclohexyl protons), 1.728 (2H, m, cyclohexyl protons), 1.584 (1H, m, cyclohexyl proton), and 1.400-1.117 (5H, m, cyclohexyl protons).

$^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 270 MHz):  $\delta$  = 159.191, 153.745, 147.873, 115.276, 113.126, 49.245, 31.840, 24.732, and 24.443.

20

### Example 4

#### Synthesis of

#### 5-(1-Piperidylcarbonyl)furan-2-sulfonic Acid Sodium Salt

The title compound was prepared from 1-(2-furoyl)piperidine and sulfur trioxide pyridine complex using the procedure described in Example 1 above. The title compound was isolated in 54.0% yield as a solid, m.p. = 286.4°C (dec) ( $R_f$  = 0.31 on a silica gel plate using 2:1 EtOAc/EtOH).

25

Spectroscopic data were as follows:

IR (KBr,  $\text{cm}^{-1}$ ): 3453.5 (broad, hydrate & NH), 2938.9 (CH), 1620.2 (C=O), 1573.5 (furan ring), 1240 ( $\text{SO}_2$ ), 1220.9 ( $\text{SO}_2$ ), and 1049.8 ( $\text{SO}_3$ ).

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<sup>1</sup>H NMR (D<sub>2</sub>O, 270 MHz):  $\delta$  = 6.995 (1H, d,  $J$ =3.6 Hz, furan CH), 6.942 (1H, d,  $J$ =3.6 Hz, furan CH), 3.723 (2H, m, CH<sub>2</sub>), 3.625 (2H, m, CH<sub>2</sub>), and 1.668 (6H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>).

<sup>13</sup>C NMR (D<sub>2</sub>O, 270 MHz):  $\delta$  = 160.228, 153.120, 147.476, 116.252, 112.637, 48.558, 44.455, 25.968, 25.114, and 23.512.

### Example 5

#### Synthesis of 5-[2-(*N*-*n*-Butylcarbamoyl)eth-1-enyl]- furan-2-sulfonic Acid Sodium Salt

10

To a suspension of (*N*-*n*-butylcarbamoyl)methyltriphenylphosphonium chloride (16.63 g, 40.38 mmol), from Example B above, in tetrahydrofuran (200 mL) at 0-5 °C was added a solution of *n*-butyllithium in hexanes (18 mL, 2.5 M, 45 mmol). Upon addition of the *n*-butyllithium solution, the solution became homogeneous and the reaction mixture was stirred for 10 min at 5 °C. 5-Formylfuran-2-sulfonic acid sodium salt (8.0 g, 40.38 mmol) was then added in one portion and the reaction mixture was stirred for 45 min at 0-5 °C and then at room temperature for 1.75 h. The mixture was filtered and the solid obtained was stirred with THF (100 mL) for several hours and then filtered. The solid was mixed with ethanol (200 mL) and filtered to remove the undissolved solid. Removal of solvent provided 8.24 g (69.1% yield) of the title compound as a slightly yellowish powder, m.p. = 318.1 °C (dec) ( $R_f$  = 0.55 on a silica gel plate using 2:1 EtOAc/EtOH). This product consisted of 70% *trans*-isomer and 30% *cis*-isomer.

25

Spectroscopic data were as follows:

IR (KBr, cm<sup>-1</sup>): 3423.1 (broad, hydrate and NH), 2960 (CH), 1662 and 1654 (C=O of two isomers), 1574 (furan ring), 1552 (NH), 1242.9 (SO<sub>2</sub>), 1209.1 (SO<sub>2</sub>), and 1045.0 (SO<sub>3</sub>).

30

<sup>1</sup>H NMR (D<sub>2</sub>O, 270 MHz):  $\delta$  = 7.157 (0.7H, d,  $J$ =15.6 Hz, vinyl CH of *trans*-isomer), 6.816-6.733 (1.3H, m, furan CH of *trans*-isomer and furan CH of *cis*-isomer), 6.657 (0.7H, d,  $J$ =3.5 Hz, furan CH of *trans*-isomer), 6.517 (0.3H, d,  $J$ =12.6 Hz, vinyl CH of *cis*-isomer), 6.430 (0.7H, d,  $J$ =15.6 Hz, vinyl CH of *trans*-

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isomer), 5.938 (0.3H, d,  $J=12.6$  Hz, vinyl CH of *cis*-isomer) 3.153 (2H, m,  $\text{NCH}_2$  of *trans* and *cis* isomers), 1.415 (2H, m,  $\text{CH}_2$  of *trans* and *cis* isomers), 1.238 (2H, m,  $\text{CH}_2$  of *trans* and *cis* isomers), and 0.813 (3H, t,  $J=7.3$  Hz,  $\text{CH}_3$  of *trans* and *cis* isomers).

5  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 270 MHz):  $\delta = 169.853, 168.297, 152.723, 152.540, 152.189, 151.854, 127.143, 123.116, 122.461, 120.767, 114.529, 113.766, 113.629, 39.269, 30.254, 29.980, 19.287, 19.195, \text{ and } 12.698.$

### Example 6

10

#### Synthesis of 5-[2-(*N-n*-Butylcarbamoyl)ethyl]- furan-2-sulfonic Acid Sodium Salt

The title compound was prepared by hydrogenation of the product from Example 5 above using Pd/C at room temperature in ethanol in a Parr pressure  
15 reactor. The title compound was isolated in 28.8% yield as a solid, m.p. =  $184.9^\circ\text{C}$  (dec) ( $R_f = 0.45$  on a silica gel plate using 2:1 EtOAc/EtOH).

Spectroscopic data were as follows:

IR (KBr,  $\text{cm}^{-1}$ ): 3432 (broad, hydrate & NH), 2960 (CH), 1637.2 (C=O), 1560.7 (NH), 1520.6 (furan ring), 1228.7 ( $\text{SO}_2$ ), 1204.8 ( $\text{SO}_2$ ), and 1044.5 ( $\text{SO}_3$ ).

20  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 270 MHz):  $\delta = 6.727$  (1H, d,  $J=3.3$  Hz, furan CH), 6.182 (1H, d,  $J=3.3$  Hz, furan CH), 3.087 (2H, t,  $J=6.7$  Hz,  $\text{NCH}_2$ ), 2.969 (2, t,  $J=6.9$  Hz,  $\text{CH}_2$ ), 2.563 (2H, t,  $J=6.9$  Hz,  $\text{CH}_2\text{CO}$ ), 1.340 (2H, m,  $\text{CH}_2$ ), 1.183 (2H, m,  $\text{CH}_2$ ), and 0.807 (3H, t,  $J=7.3$  Hz,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 270 MHz):  $\delta = 175.069, 157.101, 150.435, 112.820,$   
25  $107.375, 38.949, 33.854, 30.285, 23.832, 19.119, \text{ and } 12.804.$

### Example 7

#### Synthesis of *N-n*-Butyl-5-(*N-n*-butylcarbamoyl)furan-2-sulfonamide

30 A suspension of 5-formyl-2-furansulfonic acid sodium salt (90 g, 0.454 mol) and potassium dichromate (89.1 g, 0.303 mol) in water (350 mL) was heated to reflux. With the heat off, a solution of sulfuric acid (98%, 55 mL) and water (50 mL) was added dropwise for 40 min. The reaction mixture was refluxed for an

-- 40 --

additional 3 hours and then cooled to room temperature. The pH of the reaction mixture was adjusted to about 10 with potassium hydroxide. After filtration, the filtrate was concentrated to ca. 200 mL. Chromatography of the residue on silica gel using methanol as the eluant gave 43.5 g of crude 5-carboxy-2-furansulfonic acid sodium/potassium salt.

A portion of salt (20.0 g, 79.3 mmol) was mixed with  $\text{POCl}_3$  (40 mL) at 5-10°C.  $\text{PCl}_5$  (40 g) was added in portions to the mixture. After stirred for 1 hour at room temperature, the mixture was filtered and the solid was washed with  $\text{CH}_2\text{Cl}_2$ . Rotary evaporation of the filtrate gave 14.8 g of crude 5-chlorocarbonyl-2-furansulfonyl chloride.

To a solution of this dichloride in  $\text{CH}_2\text{Cl}_2$  (150 mL) was added dropwise a solution of *n*-butylamine (38 mL) in  $\text{CH}_2\text{Cl}_2$  (50 mL) at 5-10°C. This mixture was stirred at room temperature for additional 18 hours and then poured into wet-ice (200 g). After conc. hydrochloric acid (6 mL) was added, the mixture was separated and the organic layer was washed with water (2 x 200 mL). The solution was dried over sodium sulfate, filtered and evaporated. Removal of solvent provided the title compound (8.42 g, 13.3% overall yield) as a solid, m.p. = 69.4°C ( $R_f$ =0.63 on a silica gel plate using EtOAc as an eluant).

Spectroscopic data were as follows:

IR (KBr,  $\text{cm}^{-1}$ ): 3382.9 (NH), 2962 (CH), 2934 (CH), 2872 (CH), 1656.0 (C=O), 1596.6 (furan ring), 1539.7 (NH), 1340.7 ( $\text{SO}_2$ ) and 1183.3 ( $\text{SO}_2$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz):  $\delta$  = 7.123 (1H, d,  $J$  = 3.6 Hz, furan CH), 7.045 (1H, d,  $J$  = 3.6 Hz, furan CH), 6.576 (1H, t,  $J$  = 5.2 Hz, COHN), 5.098 (1H, t,  $J$  = 5.9 Hz,  $\text{NHSO}_2$ ), 3.398 (2H, q,  $J$  = 6.8 Hz,  $\text{CH}_2$ ), 3.030 (2H, q,  $J$  = 6.7 Hz,  $\text{CH}_2$ ), 1.620-1.216 (8H, m, 2  $\text{CH}_2\text{CH}_2$ ), 0.923 (3H, t,  $J$  = 7.3 Hz,  $\text{CH}_3$ ) and 0.848 (3H, t,  $J$  = 7.2 Hz,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 270 MHz):  $\delta$  = 157.437, 150.725, 149.215, 117.534, 114.437, 42.853, 38.933, 31.230, 19.668, 19.195, 13.262 and 13.033.

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## Example 8

## Synthesis of

*N,N*-Diethyl-5-(*N,N*-diethylcarbamoyl)furan-2-sulfonamide

5 The procedure described in Example 7 was employed for the preparation of the title compound using diethylamine instead of *n*-butylamine. The title compound was separated in 5.9% overall yield as a solid, m.p. 56.4°C ( $R_f$  = 0.22 on a silica gel plate using EtOAc/hexanes, 1:1, v:v, as the eluant).

Spectroscopic data were as follows:

10 IR (KBr,  $\text{cm}^{-1}$ ): 2978 (CH), 2938 (CH), 1631.3 (C=O), 1571.6 (furan ring), 1360.6 ( $\text{SO}_2$ ) and 1171.0 ( $\text{SO}_2$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz):  $\delta$  = 7.004 (1H, d,  $J$  = 3.6 Hz, furan CH), 6.958 (1H, d,  $J$  = 3.6 Hz, furan CH), 3.499 (4H, broad m, 2  $\text{CH}_2$ ), 3.289 (4H, q,  $J$  = 7.2 Hz, 2  $\text{CH}_2$ ), 1.224 (6H, broad m, 2  $\text{CH}_3$ ) and 1.145 (6H, t,  $J$  = 7.2 Hz, 2  $\text{CH}_3$ ).

15  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 270 MHz):  $\delta$  = 158.825, 151.228, 149.840, 116.130, 42.609, 42.198, 14.421, 13.857 and 112.225.

Using the procedures described in Examples 1-8 above and the appropriate starting materials and reagents, the following additional furansulfonic acid derivatives of formula I can be prepared:

- 20 *N*-methyl-5-carbamoylfuran-2-sulfonic acid  
*N*-ethyl-5-carbamoylfuran-2-sulfonic acid  
*N*-*n*-propyl-5-carbamoylfuran-2-sulfonic acid  
*N*-isobutyl-5-carbamoylfuran-2-sulfonic acid  
*N*-*sec*-butyl-5-carbamoylfuran-2-sulfonic acid  
25 *N*-*tert*-butyl-5-carbamoylfuran-2-sulfonic acid  
*N*-*n*-pentyl-5-carbamoylfuran-2-sulfonic acid  
*N*-cyclopentyl-5-carbamoylfuran-2-sulfonic acid  
*N*-*n*-hexyl-5-carbamoylfuran-2-sulfonic acid  
*N*-*n*-octyl-5-carbamoylfuran-2-sulfonic acid  
30 *N*-*tert*-octyl-5-carbamoylfuran-2-sulfonic acid  
*N*-phenyl-5-carbamoylfuran-2-sulfonic acid  
5-(1-pyrrolidinylcarbonyl)furan-2-sulfonic acid

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- 5-(4-morpholinylcarbonyl)furan-2-sulfonic acid  
*N*-methyl-4-carbamoylfuran-2-sulfonic acid  
*N*-ethyl-4-carbamoylfuran-2-sulfonic acid  
*N*-*n*-propyl-4-carbamoylfuran-2-sulfonic acid  
5 *N*-isopropyl-4-carbamoylfuran-2-sulfonic acid  
*N*-*n*-butyl-4-carbamoylfuran-2-sulfonic acid  
*N*-isobutyl-4-carbamoylfuran-2-sulfonic acid  
*N*-*sec*-butyl-4-carbamoylfuran-2-sulfonic acid  
*N*-*tert*-butyl-4-carbamoylfuran-2-sulfonic acid  
10 *N*-*n*-pentyl-4-carbamoylfuran-2-sulfonic acid  
*N*-cyclopentyl-4-carbamoylfuran-2-sulfonic acid  
*N*-*n*-hexyl-4-carbamoylfuran-2-sulfonic acid  
*N*-cyclohexyl-4-carbamoylfuran-2-sulfonic acid  
*N*-*n*-octyl-4-carbamoylfuran-2-sulfonic acid  
15 *N*-*tert*-octyl-4-carbamoylfuran-2-sulfonic acid  
*N*-phenyl-4-carbamoylfuran-2-sulfonic acid  
4-(1-piperidylcarbonyl)furan-2-sulfonic acid  
4-(1-pyrrolidinylcarbonyl)furan-2-sulfonic acid  
4-(4-morpholinylcarbonyl)furan-2-sulfonic acid  
20 *N,N*-dimethyl-5-carbamoylfuran-2-sulfonic acid  
*N,N*-diethyl-5-carbamoylfuran-2-sulfonic acid  
*N,N*-di-*n*-propyl-5-carbamoylfuran-2-sulfonic acid  
*N,N*-diisopropyl-5-carbamoylfuran-2-sulfonic acid  
*N,N*-di-*n*-butyl-5-carbamoylfuran-2-sulfonic acid  
25 *N,N*-diisobutyl-5-carbamoylfuran-2-sulfonic acid  
*N,N*-di-*sec*-butyl-5-carbamoylfuran-2-sulfonic acid  
*N*-ethyl-*n*-methyl-5-carbamoylfuran-2-sulfonic acid  
*N*-*n*-propyl-*N*-methyl-5-carbamoylfuran-2-sulfonic acid  
*N*-isopropyl-*N*-methyl-5-carbamoylfuran-2-sulfonic acid  
30 *N*-*n*-butyl-*N*-methyl-5-carbamoylfuran-2-sulfonic acid  
*N*-cyclohexyl-*N*-methyl-5-carbamoylfuran-2-sulfonic acid  
*N*-ethyl-*N*-*n*-propyl-5-carbamoylfuran-2-sulfonic acid

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- N*-ethyl-*N*-isopropyl-5-carbamoylfuran-2-sulfonic acid  
*N*-ethyl-*N*-*n*-butyl-5-carbamoylfuran-2-sulfonic acid  
*N*-ethyl-*N*-cyclohexyl-5-carbamoylfuran-2-sulfonic acid  
5 5-[2-(*N*-methylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid  
5-[2-(*N*-ethylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid  
5-[2-(*N*-*n*-propylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid  
5-[2-(*N*-isopropylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid  
5-[2-(*N*-isobutylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid  
5-[2-(*N*-*tert*-butylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid  
10 5-[2-(*N*-cyclohexylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid  
5-[2-(*N,N*-dimethylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid  
5-[2-(*N*-methylcarbamoyl)ethyl]furan-2-sulfonic acid  
5-[2-(*N*-ethylcarbamoyl)ethyl]furan-2-sulfonic acid  
5-[2-(*N*-*n*-propylcarbamoyl)ethyl]furan-2-sulfonic acid  
15 5-[2-(*N*-isopropylcarbamoyl)ethyl]furan-2-sulfonic acid  
5-[2-(*N*-isobutylcarbamoyl)ethyl]furan-2-sulfonic acid  
5-[2-(*N*-*tert*-butylcarbamoyl)ethyl]furan-2-sulfonic acid  
5-[2-(*N*-cyclohexylcarbamoyl)ethyl]furan-2-sulfonic acid  
5-[2-(*N,N*-dimethylcarbamoyl)ethyl]furan-2-sulfonic acid  
20 *N*-methyl-5-(*N*-methylcarbamoyl)furan-2-sulfonamide  
*N*-ethyl-5-(*N*-ethylcarbamoyl)furan-2-sulfonamide  
*N*-*n*-propyl-5-(*N*-*n*-propylcarbamoyl)furan-2-sulfonamide  
*N*-*iso*-propyl-5-(*N*-*iso*-propylcarbamoyl)furan-2-sulfonamide  
*N*-*tert*-butyl-5-(*N*-*tert*-butylcarbamoyl)furan-2-sulfonamide  
25 *N*-cyclopentyl-5-(*N*-cyclopentylcarbamoyl)furan-2-sulfonamide  
*N*-*n*-hexyl-5-(*N*-*n*-hexylcarbamoyl)furan-2-sulfonamide  
*N*-cyclohexyl-5-(*N*-cyclohexylcarbamoyl)furan-2-sulfonamide,  
and the like; and pharmaceutically acceptable salts thereof.

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## Example 9

**Inhibition of A $\beta$ (1-40) Beta-Pleated Sheet Formation**

Thioflavin T (ThT) is known to rapidly associate with beta-pleated sheets, particularly the aggregated fibrils of synthetic A $\beta$ (1-40). This association gives rise to a new excitation maximum at 440 nm and to enhanced emission at 490 nm. In this experiment, the ability of the compounds prepared in Examples 1, 2 and 6 above to inhibit the association of ThT with synthetic A $\beta$ (1-40) is demonstrated by measuring changes in fluorescence.

The experiments were performed using a CytoFluor II fluorescence plate reader having the following parameters:

Filters:	Excitation 440 nm/20 Emission 490 nm/40
Gain:	75
Cycle to Cycle Time:	30 min
Run Time:	720 min (24 cycles) or dependent on experimental design
Plate:	96 well

Into each well was aliquoted 95  $\mu$ l of ThT (3  $\mu$ M) prepared in PBS (pH 6.0), 2  $\mu$ L of the compound to be tested (10  $\mu$ M) prepared with 0.05% of methylcellulose in PBS (pH 6.0), and 3  $\mu$ L of A $\beta$ (1-40) (3  $\mu$ g) prepared with dH<sub>2</sub>O. The fluorescence measurement began when the A $\beta$ (1-40) was added and continued for a total of 12-24 hours. The percent inhibition of beta-pleated sheet formation was calculated from the relative fluorescence unit increase over the 12-24 hours between aggregation in the presence and in the absence of the test compounds. The data show that the compounds prepared in Examples 1, 2 and 6 above inhibited A $\beta$ (1-40) beta-pleated sheet formation at least 10% compared to the controls.

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## Example 10

**Protection Against A $\beta$ (25-35)-Induced Neuronal Cell Loss**

In this experiment, the ability of the compounds prepared in Examples 1, 2 and 5 above to protect against A $\beta$ (25-35)-induced neuronal cell loss is demonstrated. Sprague Dawley rat hippocampus of 18-day-gestation embryos was excised and then dissociated by trituration to prepare primary neuronal/astrocytic cultures. Cells ( $3 \times 10^5$ ) were plated on 35 mm poly-D-lysine-coated plates containing Eagle's minimum essential medium supplemented with 10% fetal bovine serum. After 3-5 hours, the original medium was removed and replaced with 1 mL of fresh medium. Cultures were maintained at 37°C in a 5% CO<sub>2</sub>/95% air, humidified incubator.

To the cells (7 DIV) was added 30  $\mu$ M of A $\beta$ (25-35) dissolved in dH<sub>2</sub>O (stored at -20°C) and 100  $\mu$ M of the test compound in 1% methylcellulose. Controls were also conducted without the test compound. The percentage of morphologically viable neurons was determined counting the number of viable neurons after 96 hours treatment compared to the number of neurons before treatment in the same premarked culture regions (three regions/culture). The number of wells was n = 6 per treatment condition. The data show that the compounds prepared in Example 1, 2 and 5 above reduce A $\beta$ (25-35)-induced neuronal cell loss by at least 60% compared to the controls.

## Example 11

**Reduction of  $\beta$ -Amyloid-Induced Increased Release of Interleukin-1 $\beta$ , Interleukin-6 and Tumor Necrosis Factor- $\alpha$** 

In this experiment, the ability of the compounds prepared in Examples 1, 2, 5 and 6 above to reduce the LPS and  $\beta$ -amyloid-induced increased release of interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) is demonstrated. THP-1 cells, a human monocyte cell line from American Type Culture Collection, were grown in RPMI-1640 medium plus 10% fetal bovine serum (FBS, not heat-inactivated) in T-flasks. The medium was changed every two days by spinning down (800 rpm, 5 minutes) the cells, replating cells and



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adding fresh medium. Alternatively, the cultures were maintained by the addition of fresh medium. The cultures were maintained at a cell concentration ranging from between  $1 \times 10^5$  and  $1 \times 10^6$  cells/mL. Because sera may contain unknown factors which can affect macrophage/monocyte IL-1 production, the FBS was  
5 reduced to 5% for 24 hours. The FBS was further reduced to 2% over two days prior to starting each experiment. The cells were collected by centrifugation and resuspended into 2% FBS. Cell numbers were calculated and cells were plated on 24-well plates ( $3 \times 10^5$  cells/0.6 mL/well). Cells were then treated with LPS ( $0.5 \mu\text{g/ml}$  or  $0-10 \mu\text{g/ml}$  for LPS dose-response experiments) alone or in combination  
10 with A $\beta$  peptides ( $5 \mu\text{M}$  or  $0.05-5 \mu\text{M}$  for dose-response experiments). When determining the effect of the test compounds on IL-1 $\beta$ , IL-6 and TNF $\alpha$  release,  $100 \mu\text{M}$  of the test compound was added with the LPS and A $\beta$ (25-35) and this mixture was incubated for 48 hours prior to performing ELISA.

15 IL-1 $\beta$ , IL-6 and TNF $\alpha$  secretions into medium by LPS-stimulated THP-1 cells, in the presence or absence of amyloid peptides and a test compound, were assayed with a commercially available ELISA kit (R & D Systems). Briefly, a microtiter plate coated with a murine monoclonal antibody to human IL-1 $\beta$ , IL-6, or TNF $\alpha$  was supplied by the manufacturer. Standards and samples were pipetted  
20 into the wells and any IL-1 $\beta$ , IL-6 or TNF $\alpha$  present was bound by the immobilized antibody. Unbound proteins were washed away and a horseradish peroxidase-linked polyclonal antibody specific for IL-1 $\beta$ , IL-6 or TNF $\alpha$  was added to the wells to "sandwich" the IL-1 $\beta$ , IL-6 and TNF $\alpha$  bound in the initial step. After washing to remove any unbound antibody-enzyme reagent, a substrate solution  
25 (1:1 hydrogen peroxide:tetramethylbenzidine, v/v) was added to the wells and color developed in proportion to the amount of IL-1 $\beta$ , IL-6 or TNF $\alpha$  bound in the initial step. Color development was stopped with 2 N sulfuric acid and the optical density of the standard and the test samples was measured at 450 nm. The amounts of IL-1 $\beta$ , IL-6 or TNF $\alpha$  present in the samples were calculated based  
30 upon a standard curve. Assays were run in quadruplicate wells. The data show that the compounds prepared in Example 1, 2, 5 and 6 above reduced the  $\beta$ -

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amyloid-induced increased release of interleukin-1 $\beta$ , interleukin-6 and tumor necrosis factor- $\alpha$  by at least 20% compared to the controls.

#### Example 12

##### 5                    **Reduction of Locomotor Impairment Due to A $\beta$ -Peptide**

In this experiment, the ability of the compound prepared in Example 1 above to reduce the *in vivo* impairment of animals treated with A $\beta$ -peptide is demonstrated. Male Sprague-Dawley rats (250-400 g) were given injections of 20  $\mu$ g of A $\beta$ (25-35) into their substantia nigra. Prior to the injection, the rats were  
10    fasted overnight and then each received an oral treatment of the test compound (1-10 mg/kg) dissolved in aqueous 1% methyl cellulose or the vehicle alone, one hour before and three hours post the A $\beta$ -peptide stereotaxic injection. One week after treatment, the rats were dosed s.c. with 0.5 mg/kg apomorphine (dissolved in 0.1% vitamin C in isotonic saline) and the circling reflex was monitored using a Rotorat  
15    computerized behavioral monitoring apparatus for the time period between 15 and 30 minutes of being placed in the arena. Impairment of the animals due to A $\beta$ -peptide was determined by measuring the number of rotations over the 15 minute period. The data show that the compound of Example 1 above reduced the locomotor impairment of rats injected with A $\beta$ (25-35) compared to A $\beta$ (25-35)-  
20    treated controls.

#### Example 13

##### **Reduction of Cognitive Deficits in Autoimmune Mice**

In this experiment, the ability of the compound prepared in Example 1  
25    above to reduce cognitive deficits in autoimmune strains of mice is demonstrated. MRL/MpJfas<sup>lpr</sup> ("mutant mice" or "Fas<sup>lpr</sup>") strains of mice have been described as useful models of Lupus due to their autoimmune lymphoproliferatory pathology. In particular, the mutant mice show a cognitive deficit at approximately four months of age, which is not observed at two months of age. See, for example,  
30    Forster et al., 1988, *Behav. Neural Biology*, 49, 139-151.

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In the experiment, wild-type ("++") and Fas<sup>lpr</sup> strains of mice were received at 4 to 8 weeks of age (n = 10-11). The compound of Example 1 above or 1% methylcellulose (100 mg/kg p.o.) was administered daily from 2 months of age to 4 months of age (a total of 9 weeks). After reaching 4 months of age, the mice were tested for cognitive ability in a T-maze. This behavioral task measures discrimination, active avoidance and acquisition skills (acquisition is the number of avoidances in the first 5 test trials). The Fas<sup>lpr</sup> mice showed a deficit in both avoidance and acquisition compared to the wild-type mice which received the 1% methylcellulose. In contrast, the Fas<sup>lpr</sup> mice treated with the compound of Example 1-above had reduced avoidance-values and acquired avoidance skills earlier than untreated mutant mice (i.e., similar to the wild-type controls). The data for acquisition and avoidance are shown in Figures 1 and 2, respectively. These results demonstrate that the compound prepared in Example 1 above reduced the cognitive deficits of the autoimmune mutant strain of mice.

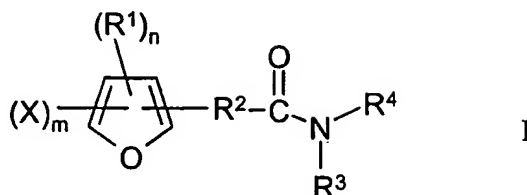
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From the foregoing description, various modifications and changes in the compositions and methods of this invention will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

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**WHAT IS CLAIMED IS:**

1. A compound of formula I:



10 wherein

each  $R^1$  is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

15  $R^2$  is selected from the group consisting of alkylene, alkenylene and a covalent bond;

$R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that  $R^3$  and  $R^4$  are not both hydrogen; or  $R^3$  and  $R^4$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a

20 heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

each X is independently selected from the group consisting of  $-SO_3Y$  and  $-SO_2NR^5R^6$ , wherein Y is hydrogen or a pharmaceutically acceptable cation, and  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl,

25 alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl; or  $R^5$  and  $R^6$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

$m$  is an integer from 1 to 3; and  $n$  is an integer from 0 to 2, provided that  $m$

30  $+ n = 3$ .

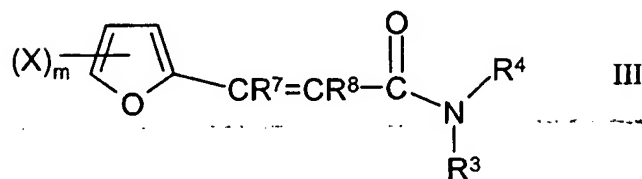
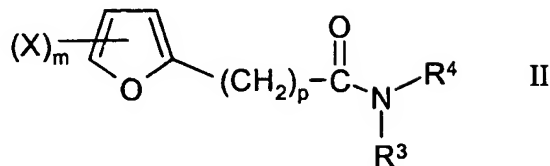
2. The compound according to Claim 1 wherein  $R^1$  is hydrogen.

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3. The compound according to Claim 1 wherein  $R^2$  is selected from the group consisting of an alkylene group of the formula  $-(CH_2)_p-$ , wherein  $p$  is an integer from 1 to 6; an alkenylene group of the formula  $-CR^7=CR^8-$ , wherein  $R^7$  and  $R^8$  are independently selected from the group consisting of hydrogen and lower alkyl; and a covalent bond.
4. The compound according to Claim 3 wherein  $R^2$  is selected from the group consisting of  $-CH_2CH_2-$ ,  $-CH=CH-$  and a covalent bond.
5. The compound according to Claim 1 wherein  $R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, provided that  $R^3$  and  $R^4$  are not both hydrogen; or  $R^3$  and  $R^4$  are joined together to form a cycloalkyl group having 4 or 6 carbon atoms.
6. The compound according to Claim 5 wherein  $R^3$  is hydrogen and  $R^4$  is lower alkyl or cycloalkyl.
7. The compound according to Claim 1 wherein  $X$  is  $-SO_3Y$ .
8. The compound according to Claim 1 wherein  $X$  is  $-SO_2NR^5R^6$ , wherein  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl and cycloalkyl; or  $R^5$  and  $R^6$  are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms.
9. The compound according to Claim 8 wherein  $R^5$  is hydrogen and  $R^6$  is selected from the group consisting of hydrogen, alkyl and cycloalkyl.
10. The compound according to Claim 1 wherein  $m$  is 1.

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11. A compound of formula II or III:



wherein

15  $R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that  $R^3$  and  $R^4$  are not both hydrogen; or  $R^3$  and  $R^4$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

20 each X is independently selected from the group consisting of  $-SO_3Y$  and  $-SO_2NR^5R^6$ , wherein Y is hydrogen or a pharmaceutically acceptable cation, and  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl; or  $R^5$  and  $R^6$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

$R^7$  and  $R^8$  are independently selected from the group consisting of hydrogen and lower alkyl;

$m$  is an integer from 1 to 3; and  $p$  is an integer from 0 to 6.

30

12. The compound according to Claim 11 wherein  $R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl and

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cycloalkyl, provided that  $R^3$  and  $R^4$  are not both hydrogen; or  $R^3$  and  $R^4$  are joined together to form a cycloalkyl group having 4 or 6 carbon atoms.

13. The compound according to Claim 12 wherein  $R^3$  is hydrogen and  
5  $R^4$  is lower alkyl or cycloalkyl.

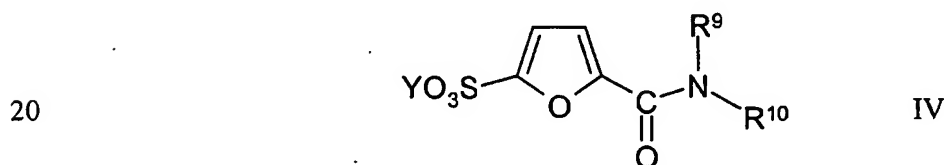
14. The compound according to Claim 11 wherein X is  $-\text{SO}_3\text{Y}$ .

15. The compound according to Claim 11 wherein  $R^7$  and  $R^8$  are  
10 hydrogen.

16. The compound according to Claim 11 wherein  $p$  is 0, 1 or 2.

17. The compound according to Claim 11 wherein  $m$  is 1.  
15

18. A compound of formula IV:



wherein

$R^9$  and  $R^{10}$  are independently selected from the group consisting of  
25 hydrogen, lower alkyl and cycloalkyl, provided that  $R^9$  and  $R^{10}$  are not both hydrogen; or  $R^9$  and  $R^{10}$  are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms; and

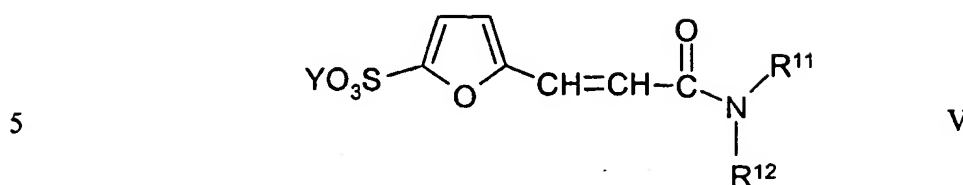
Y selected from the group consisting of hydrogen and a pharmaceutically acceptable cation.

30

19. The compound according to Claim 27 wherein Y is hydrogen or a sodium cation.

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20. A compound of formula V:



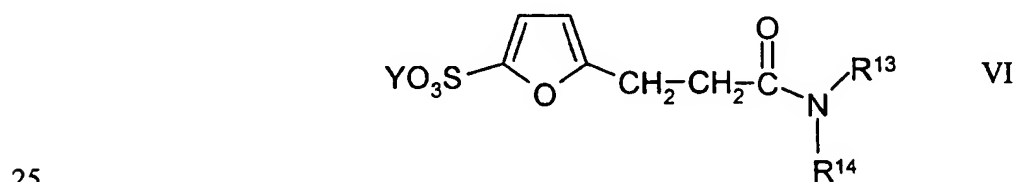
wherein

10  $R^{11}$  and  $R^{12}$  are independently selected from the group consisting of hydrogen, lower alkyl and cycloalkyl, provided that  $R^{11}$  and  $R^{12}$  are not both hydrogen; or  $R^{11}$  and  $R^{12}$  are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms; and

15 Y selected from the group consisting of hydrogen and a pharmaceutically acceptable cation.

21. The compound according to Claim 20 wherein Y is hydrogen or a sodium cation.

20 22. A compound of formula VI:



wherein

30  $R^{13}$  and  $R^{14}$  are independently selected from the group consisting of hydrogen, lower alkyl and cycloalkyl, provided that  $R^{13}$  and  $R^{14}$  are not both hydrogen; or  $R^{13}$  and  $R^{14}$  are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms; and

Y selected from the group consisting of hydrogen and a pharmaceutically acceptable cation.



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23. The compound according to Claim 22 wherein Y is hydrogen or a sodium cation.

24. A compound selected from the group consisting of:

5

*N-n*-butyl-5-carbamoylfuran-2-sulfonic acid

*N*-isopropyl-5-carbamoylfuran-2-sulfonic acid

*N*-cyclohexyl-5-carbamoylfuran-2-sulfonic acid

5-(1-piperidylcarbonyl)furan-2-sulfonic acid

5-[2-(*N-n*-butylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid

10

5-[2-(*N-n*-butylcarbamoyl)ethyl]furan-2-sulfonic acid

*N-n*-butyl-5-(*N-n*-butylcarbamoyl)furan-2-sulfonamide

*N,N*-diethyl-5-(*N,N*-diethylcarbamoyl)furan-2-sulfonamide,  
and pharmaceutically acceptable salts thereof.

15

25. The compound according to Claim 24 wherein the compound is selected from the group consisting of *N-n*-butyl-5-carbamoylfuran-2-sulfonic acid and pharmaceutically acceptable salts thereof.

20

26. The compound according to Claim 24 wherein the compound is selected from the group consisting of *N*-isopropyl-5-carbamoylfuran-2-sulfonic acid and pharmaceutically acceptable salts thereof.

25

27. The compound according to Claim 24 wherein the compound is selected from the group consisting of *N*-cyclohexyl-5-carbamoylfuran-2-sulfonic acid and pharmaceutically acceptable salts thereof.

28. The compound according to Claim 24 wherein the compound is selected from the group consisting of 5-(1-piperidylcarbonyl)furan-2-sulfonic acid and pharmaceutically acceptable salts thereof.

30

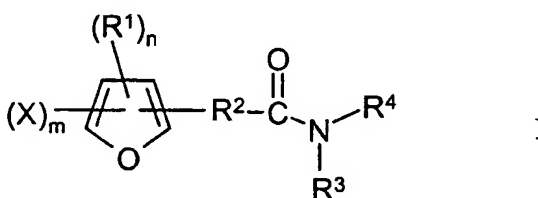
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29. The compound according to Claim 24 wherein the compound is selected from the group consisting of 5-[2-(*N*-*n*-butylcarbamoyl)eth-1-enyl]furan-2-sulfonic acid and pharmaceutically acceptable salts thereof.

5 30. The compound according to Claim 24 wherein the compound is selected from the group consisting of 5-[2-(*N*-*n*-butylcarbamoyl)ethyl]furan-2-sulfonic acid and pharmaceutically acceptable salts thereof.

10 31. The compound according to Claim 24 wherein the compound is selected from the group consisting of *N,N*-diethyl-5-(*N,N*-diethylcarbamoyl)furan-2-sulfonamide and pharmaceutically acceptable salts thereof.

15 32. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of formula I:



wherein

each  $R^1$  is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

$R^2$  is selected from the group consisting of alkylene, alkenylene and a covalent bond;

$R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that  $R^3$  and  $R^4$  are not both hydrogen; or  $R^3$  and  $R^4$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a

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heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

each X is independently selected from the group consisting of  $-\text{SO}_3\text{Y}$  and  $-\text{SO}_2\text{NR}^5\text{R}^6$ , wherein Y is hydrogen or a pharmaceutically acceptable cation, and  $\text{R}^5$  and  $\text{R}^6$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl; or  $\text{R}^5$  and  $\text{R}^6$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

$m$  is an integer from 1 to 3; and  $n$  is an integer from 0 to 2, provided that  $m + n = 3$ .

33. The pharmaceutical composition according to Claim 32 wherein  $\text{R}^1$  is hydrogen.

34. The pharmaceutical composition according to Claim 32 wherein  $\text{R}^2$  is selected from the group consisting of an alkylene group of the formula  $-(\text{CH}_2)_p-$ , wherein  $p$  is an integer from 1 to 6; an alkenylene group of the formula  $-\text{CR}^7=\text{CR}^8-$ , wherein  $\text{R}^7$  and  $\text{R}^8$  are independently selected from the group consisting of hydrogen and lower alkyl; and a covalent bond.

35. The pharmaceutical composition according to Claim 34 wherein  $\text{R}^2$  is selected from the group consisting of  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  and a covalent bond.

36. The pharmaceutical composition according to Claim 32 wherein  $\text{R}^3$  and  $\text{R}^4$  are independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, provided that  $\text{R}^3$  and  $\text{R}^4$  are not both hydrogen; or  $\text{R}^3$  and  $\text{R}^4$  are joined together to form a cycloalkyl group having 4 or 6 carbon atoms.

37. The pharmaceutical composition according to Claim 36 wherein  $\text{R}^3$  is hydrogen and  $\text{R}^4$  is lower alkyl or cycloalkyl.

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38. The pharmaceutical composition according to Claim 32 wherein X is -SO<sub>2</sub>Y.

39. The pharmaceutical composition according to Claim 32 wherein X is -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, wherein R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, alkyl and cycloalkyl; or R<sup>5</sup> and R<sup>6</sup> are joined together to form a cycloalkyl ring having 4 to 6 carbon atoms.

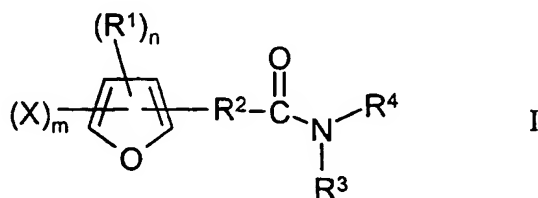
40. The pharmaceutical composition according to Claim 39 wherein R<sup>5</sup> is hydrogen and R<sup>6</sup> is selected from the group consisting of hydrogen, alkyl and cycloalkyl.

41. The pharmaceutical composition according to Claim 32 wherein *m* is 1.

42. The pharmaceutical composition according to Claim 32 wherein the carrier is an oral carrier.

43. The pharmaceutical composition according to Claim 32 wherein the carrier is an injectable carrier.

44. A method for treating a patient with a neurodegenerative disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective neurodegenerative disease-treating amount of a compound of formula I:



wherein

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each  $R^1$  is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

5  $R^2$  is selected from the group consisting of alkylene, alkenylene and a covalent bond;

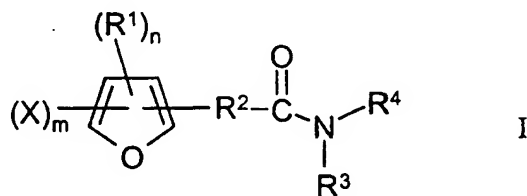
$R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that  $R^3$  and  $R^4$  are not both hydrogen; or  $R^3$  and  $R^4$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a  
10 heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

each  $X$  is independently selected from the group consisting of  $-SO_3Y$  and  $-SO_2NR^5R^6$ , wherein  $Y$  is hydrogen or a pharmaceutically acceptable cation, and  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl;  
15 or  $R^5$  and  $R^6$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

$m$  is an integer from 1 to 3; and  $n$  is an integer from 0 to 2, provided that  $m$   
20  $+ n = 3$ .

45. A method for preventing the onset of a neurodegenerative disease in a patient at risk for developing the neurodegenerative disease which method comprises administering to said patient a pharmaceutical composition comprising  
25 a pharmaceutically acceptable carrier and an effective neurodegenerative disease-preventing amount of a compound of formula I:

30



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wherein

each R<sup>1</sup> is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

5           R<sup>2</sup> is selected from the group consisting of alkylene, alkenylene and a covalent bond;

          R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that R<sup>3</sup> and R<sup>4</sup> are not both hydrogen; or R<sup>3</sup> and R<sup>4</sup> can  
10       be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

          each X is independently selected from the group consisting of -SO<sub>3</sub>Y and -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, wherein Y is hydrogen or a pharmaceutically acceptable cation, and R<sup>5</sup>  
15       and R<sup>6</sup> are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl; or R<sup>5</sup> and R<sup>6</sup> can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

20       m is an integer from 1 to 3; and n is an integer from 0 to 2, provided that m + n = 3.

46.     The method according to Claim 44 or 45 wherein the neurodegenerative disease is Alzheimer's disease.

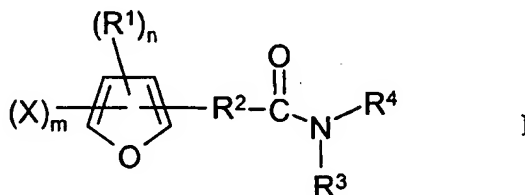
25

47.     The method according to Claim 44 or 45 wherein the neurodegenerative disease is Parkinson's disease.

48.     The method according to Claim 44 or 45 wherein the  
30       neurodegenerative disease is HIV dementia.

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49. A method for treating a patient with an autoimmune disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective autoimmune disease-treating amount of a compound of formula I:



10

wherein

each R<sup>1</sup> is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

15

R<sup>2</sup> is selected from the group consisting of alkylene, alkenylene and a covalent bond;

20

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that R<sup>3</sup> and R<sup>4</sup> are not both hydrogen; or R<sup>3</sup> and R<sup>4</sup> can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

25

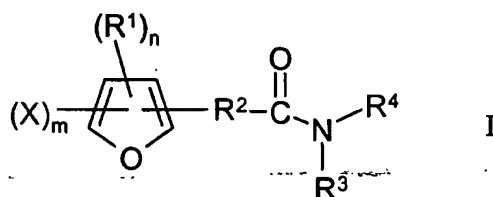
each X is independently selected from the group consisting of -SO<sub>3</sub>Y and -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, wherein Y is hydrogen or a pharmaceutically acceptable cation, and R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl; or R<sup>5</sup> and R<sup>6</sup> can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

30

m is an integer from 1 to 3; and n is an integer from 0 to 2, provided that m + n = 3.

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50. A method for preventing the onset of an autoimmune disease in a patient at risk for developing the autoimmune disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective autoimmune disease-preventing amount of a compound of formula I:



wherein

- each  $R^1$  is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

$R^2$  is selected from the group consisting of alkylene, alkenylene and a covalent bond;

- $R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that  $R^3$  and  $R^4$  are not both hydrogen; or  $R^3$  and  $R^4$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

- each X is independently selected from the group consisting of  $-SO_3Y$  and  $-SO_2NR^5R^6$ , wherein Y is hydrogen or a pharmaceutically acceptable cation, and  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl; or  $R^5$  and  $R^6$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

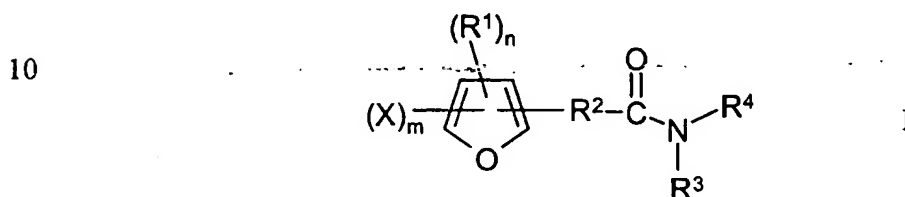
$m$  is an integer from 1 to 3; and  $n$  is an integer from 0 to 2, provided that  $m + n = 3$ .



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51. The method according to Claim 49 or 50 wherein the autoimmune disease is systemic lupus.

52. A method for treating a patient with an inflammatory disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective inflammatory disease-treating amount of a compound of formula I:



15 wherein

each  $R^1$  is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

20  $R^2$  is selected from the group consisting of alkylene, alkenylene and a covalent bond;

$R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that  $R^3$  and  $R^4$  are not both hydrogen; or  $R^3$  and  $R^4$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

25 each X is independently selected from the group consisting of  $-SO_3Y$  and  $-SO_2NR^5R^6$ , wherein Y is hydrogen or a pharmaceutically acceptable cation, and  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl; or  $R^5$  and  $R^6$  can be joined together to form a cycloalkyl ring of from 4 to 10

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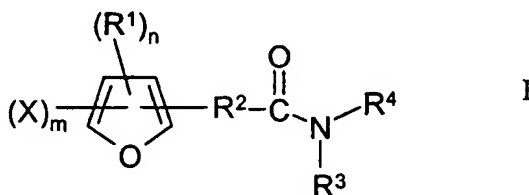
carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

$m$  is an integer from 1 to 3; and  $n$  is an integer from 0 to 2, provided that  $m + n = 3$ .

5

53. A method for preventing the onset of an inflammatory disease in a patient at risk for developing the inflammatory disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective inflammatory disease-preventing amount of a compound of formula I:

10



15

wherein

each  $R^1$  is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

20

$R^2$  is selected from the group consisting of alkylene, alkenylene and a covalent bond;

$R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that  $R^3$  and  $R^4$  are not both hydrogen; or  $R^3$  and  $R^4$  can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

25

each  $X$  is independently selected from the group consisting of  $-SO_3Y$  and  $-SO_2NR^5R^6$ , wherein  $Y$  is hydrogen or a pharmaceutically acceptable cation, and  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl;

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or R<sup>5</sup> and R<sup>6</sup> can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

5         $m$  is an integer from 1 to 3; and  $n$  is an integer from 0 to 2, provided that  $m + n = 3$ .

54.     The method according to Claim 52 or 53 wherein the inflammatory disease is rheumatoid arthritis.

10       55.     The method according to Claim 52 or 53 wherein the inflammatory disease is septic shock.

56.     The method according to Claim 52 or 53 wherein the inflammatory disease is erythema nodosum leprosy.

15

57.     The method according to Claim 52 or 53 wherein the inflammatory disease is septicemia.

20       58.     The method according to Claim 52 or 53 wherein the inflammatory disease is uveitis.

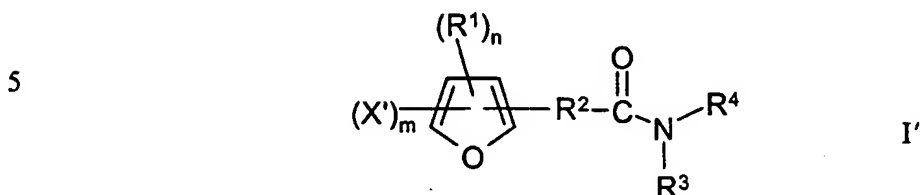
59.     The method according to Claim 52 or 53 wherein the inflammatory disease is adult respiratory distress syndrome.

25       60.     The method according to Claim 52 or 53 wherein the inflammatory disease is multiple sclerosis.

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61. A process for preparing a carbamoyl-substituted furansulfonic acid of formula I':



wherein

10 each R¹ is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl, cycloalkenyl and halo;

R² is selected from the group consisting of alkylene, alkenylene and a covalent bond;

15 R³ and R⁴ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkaryl, aryl, alkoxy, alkycycloalkyl, cycloalkyl and cycloalkenyl, provided that R³ and R⁴ are not both hydrogen; or R³ and R⁴ can be joined together to form a cycloalkyl ring of from 4 to 10 carbon atoms or a heterocyclic ring of from 4 to 10 atoms having from 1 to 3 heteroatoms selected

20 from the group consisting of oxygen, nitrogen and sulfur;

each X' is -SO₃Y, wherein Y is hydrogen or a pharmaceutically acceptable cation;

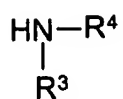
m is an integer from 1 to 3; and n is an integer from 0 to 2, provided that m + n = 3; said process comprising the steps of:

25 (a) reacting a furan carboxylic acid halide of the formula:

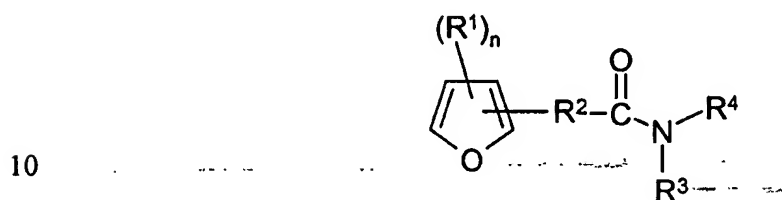


wherein R¹, R² and n are as defined above and W is chloro or bromo, with an amine of the formula:

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- 5 wherein  $\text{R}^3$  and  $\text{R}^4$  are as defined above, to provide a furan carboxamide of the formula:

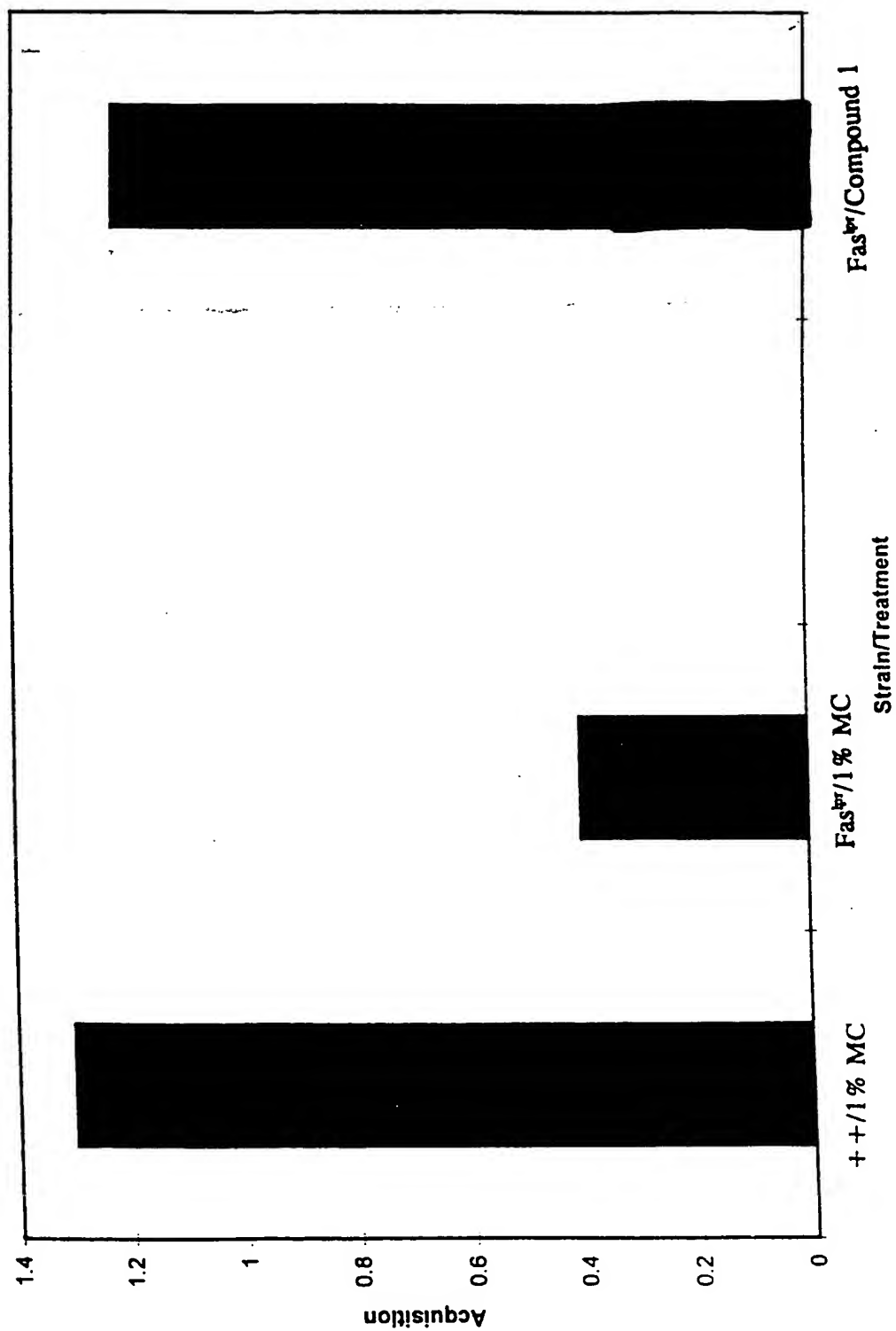


and

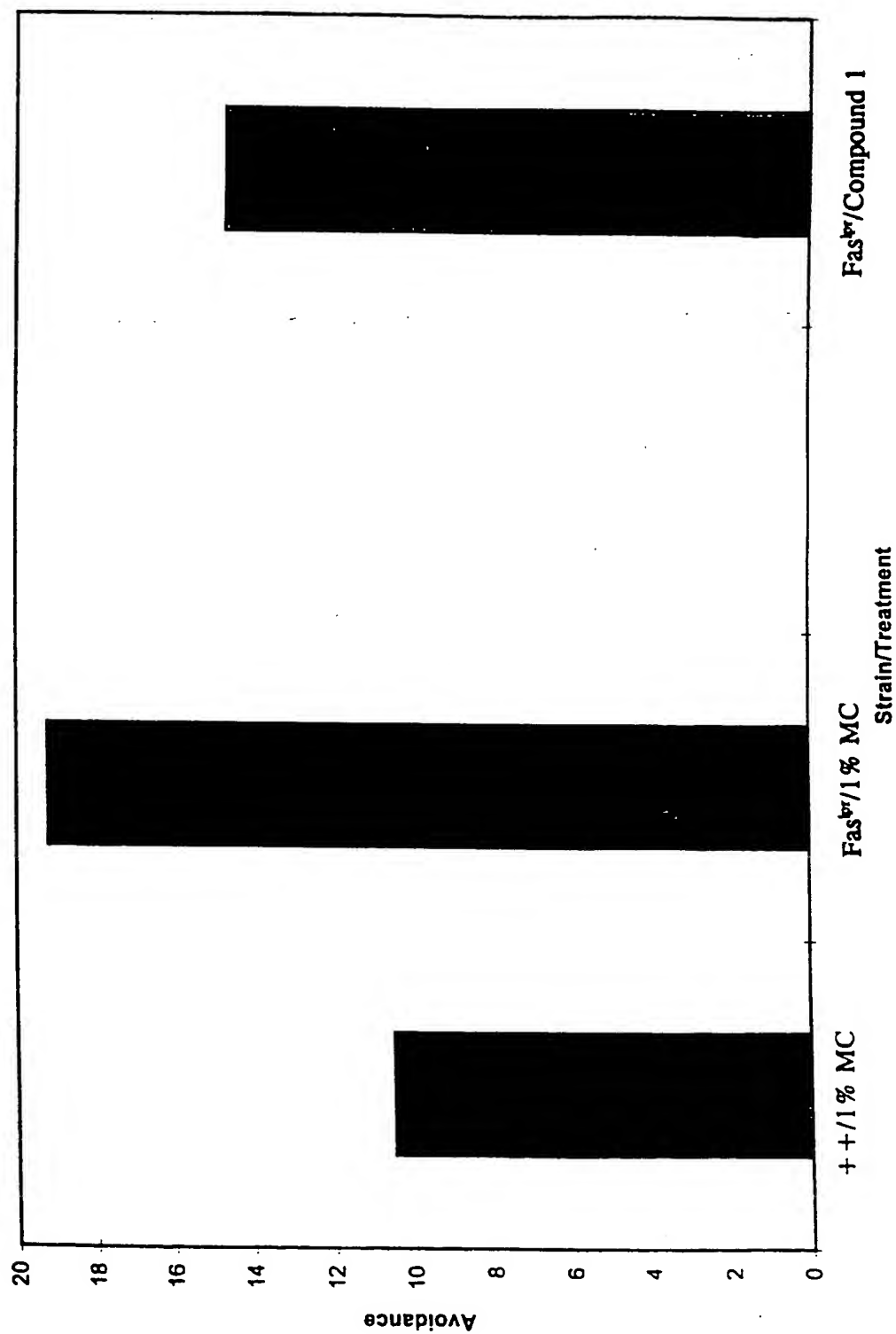
- (b) reacting the furan carboxamide with a sulfonating reagent to provide the carbamoyl-substituted furan sulfonic acid.

15

62. The process according to Claim 61 wherein the sulfonating reagent is sulfur trioxide pyridine complex.

**Fig. 1**

**Fig. 2**



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/16458

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D307/68 A61K31/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 623 592 A (STERLING WINTHROP INC.;USA) 9 November 1994 see abstract; claims see page 3, line 1 - line 39 ---	1-62
A	EP 0 676 395 A (HOECHST A.-G.;GERMANY) 11 October 1995 see page 7, line 6 - line 13 see page 24 - page 28; examples see claims 1,15-17 ---	1-62
A	WO 95 17095 A (LILLY CO ELI) 29 June 1995 see abstract; claims see examples 1,56 -----	1-62

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

4 December 1998

Date of mailing of the international search report

17/12/1998

Name and mailing address of the ISA

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Authorized officer

Paidsdor, B



# INTERNATIONAL SEARCH REPORT

I. national application No.

PCT/US 98/ 16458

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 44-60  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 44-60  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

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